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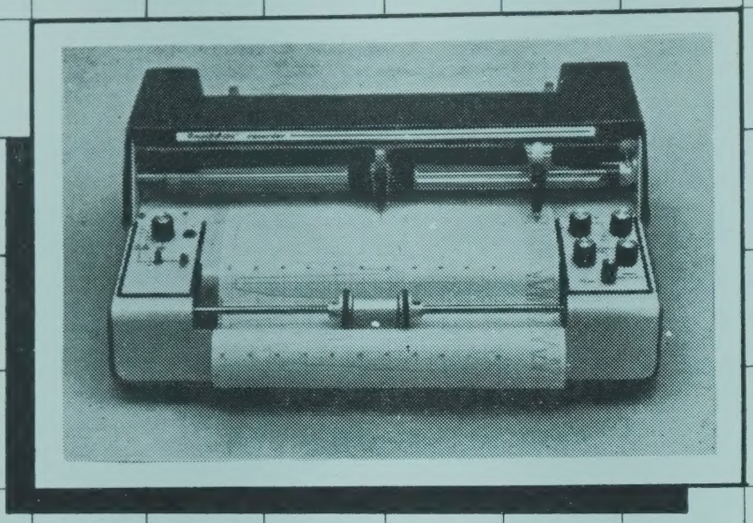

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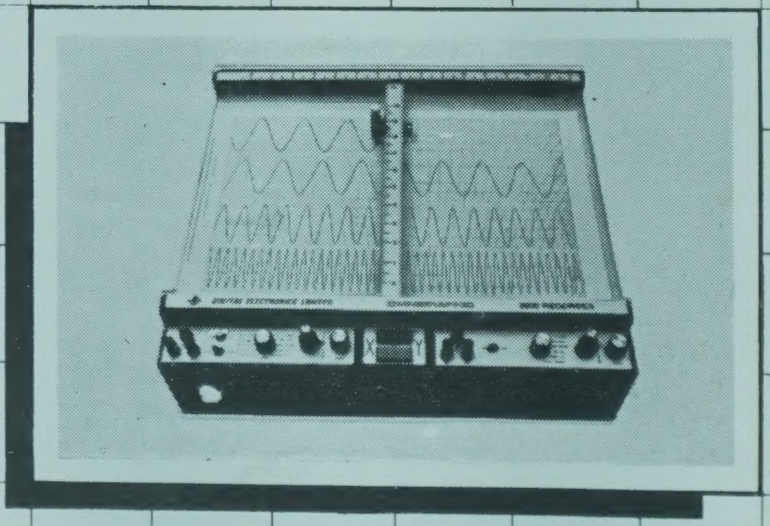

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Indian Journal of Chemistry
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Communications

Polymer Supported Reagents: Synthesis of Hippuric Acid Esters Using Anion Exchange Resin

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Polymer-supported nucleophilic reagent has been prepared by treatment of sodium salt of hippuric acid with Amberlite IRA-400 (Cl^- form). This reagent when treated with appropriate alkyl halide in ethanol furnishes the corresponding hippuric acid ester in excellent yield and in a state of high purity.

The esters of hippuric acid, in particular methyl and ethyl hippurates, have been extensively used as substrates in kinetic studies with α-chymotrypsin[1]. Hippuric acid esters are traditionally synthesised by one of the following methods: (i) acid-catalyzed esterification[2]; (ii) esterification using strong cation exchange resin as a catalyst[3]; (iii) heating an alcoholic solution of the acid in a Parr hydrogenator under H_2 atmosphere at 145°C (ref. 1) (iv) using chlorotrimethylsilane as both an acid catalyst and dehydrating agent[4]; (v) reacting appropriate alkyl halide with the acid in the presence of triethylamine[5]; (vi) esterification of hippuric acid with triethyloxonium fluoroborate in neutral or slightly basic aqueous solution at room temperature[6,7]; and (vii) esterification with triethylorthoformate in the presence of dimethylformamide[8]. The last two methods have been particularly used for the preparation of ethyl hippurate. Rehn and Ugi[9] have used isocyanides as activating agents in the synthesis of hippuric acid esters by reaction of hippuric acid with an alcohol.

As a part of our work to demonstrate the applicability of polymer-supported reagents in organic synthesis[10-13], we report herein a simple and convenient method for the synthesis of esters of hippuric acid.

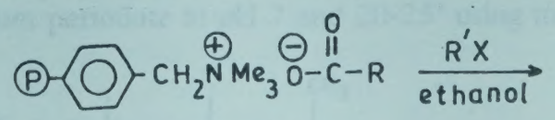
Sodium salt of hippuric acid when treated with Amberlite IRA-400 (Cl^- form) affords the polymer-supported hippuric acid anion which can be alkylated by treatment with alkyl halide in ethanol. The various esters thus prepared are listed in Table 1. The resin could be easily regenerated to its initial activity by washing with a solution of hydrochloric acid. Thus the method described here has the advantage in terms of yields and simplicity of performance. In polar solvents esterification is easy while it is difficult in non-polar solvents.

Table 1—Hippuric Acid Esters

Sl. No.	R′X	Time hr	Yield %	m.p. °C (lit) °C
1	CH_3I	11	83	81 (81-82)[1]
2	C_2H_5I	14	89	61 (58-62)[1]
3	n-C_3H_7I	15	88	59 (57-60)[1]
4	n-C_4H_9I	16	81	35 (33-35)[14]
5	$C_6H_5-CH_2-Cl$	7	90	85 (86-87)[4]
6	p-$NO_2-C_6H_5CH_2-Br$	2	93	135 (135)[5]
7	$C_2H_5COO-CH_2-Cl$	5	95	72 (71)[5]
8	$CH_3-CO-CH_2-Cl$	4	97	97 (98)[5]
9	p-$Br-C_6H_4-CO-CH_2$-Br	1	95	151 (150-51)[15]

Preparation of polymer-supported hippurate anion (I)

Strongly basic anion exchange resin in the chloride form [Amberlite IRA-400 (Cl^-)] packed in a column was washed with 0.25 *N* aqueous sodium salt of hippuric acid (prepared by dissolving 25 mmol of hippuric acid in 100 ml 0.25 *N* NaOH) until complete removal of chloride ion. The resin was successively washed with water, ethanol and ether until excess of hippuric acid anion was removed. The resin was finally dried *in vacuo* at 50°C over P_2O_5 for 10 hr. The exchange capacity was determined by passing aqueous 1 *M* sodium chloride solution (100 ml) through the 0.3 g resin in a column. The amount of hippurate anion in the eluent was titrated with 0.01 *N* hydrochloric acid using methyl orange as an indicator.



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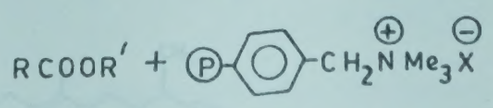

II

$R = C_6H_5CO-NH-CH_2-$

Esters of hippuric acid (II)

Amberlite IRA-400 hippurate anion (5 g; capacity 1 mmol carboxylic acid anion/g of dry resin) was placed in a flask and an appropriate quantity of alkyl halide (4.8 mmol) in ethanol was added, and the mixture was stirred at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was filtered, and the filtrate slowly distilled under reduced pressure to give the corresponding liquid hippuric acid ester, which upon standing for several days in the cold room gave large prismatic crystals in essentially pure form in quantitative yield. The products were characterised by PMR, IR and comparison with authentic samples.

One of us (M T T) is grateful to the UGC, New Delhi and Shri Swami Vivekanand Shikshan Sanstha, Kolhapur for financial assistance under the Faculty Improvement Programme.

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Pheromone Synthesis via Metallohydrazone Chemistry: Synthesis of (*E*)-6,10-Dimethyl-9-methylideneundec-5-en-2-one & (*Z*)-16-Docosen-11-one

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Carbinol(II) on treatment with LiBr via its tosylate gives 6,6-ethylenedioxy-1-bromo-2-methyl-2(*E*)-heptene(III). Alkylation of α-lithiomethyl isopropyl ketone dimethylhydrazone with III in THF at -78° followed by hydrolysis of the resulting hydrazone with $Cu(OAc)_2.H_2O$ affords V which on reaction with methylenetriphenyl phosphorane followed by deketallisation gives ketone I. Alkylation of α-lithioacetone dimethylhydrazone with nonyl bromide (VII) in THF at -78° yields VIII which on further alkylation with l-bromo-4(*Z*)-decene under similar conditions affords IX. Hydrolysis of IX with $NaIO_4$ at *p*H 7 results in the formation of pheromone (VI).

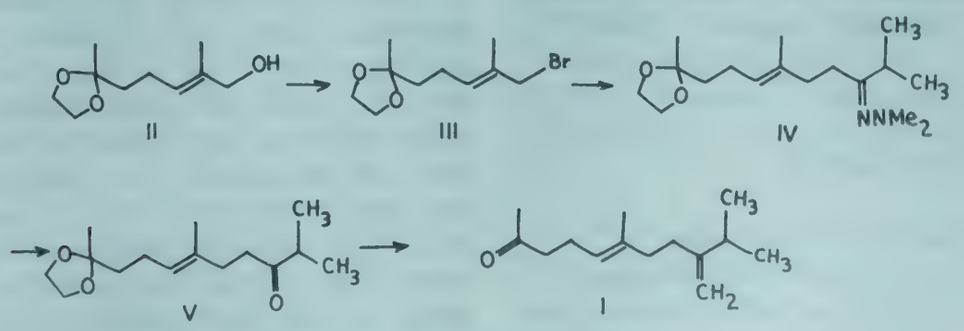
Regioselective formation of C-C bond via metallated hydrazone is well documented in the literature[1]. The keto moiety can be regenerated by hydrolysis[2] of the resulting hydrazones. In continuation of our efforts[3] on the use of α-lithiohydrazones, a group of highly reactive enolate equivalents for the construction of C-C bond regioselectively followed by mild hydrolysis of the resulting hydrazone to regenerate the ketone moiety, we wish to report herein the syntheses of pheromones (*E*)-6,10-dimethyl-9-methyleneundec-5-en-2-one(I) and (*Z*)-16-docosen-11-one(VI).

Compound(I), a C_{14}-ketone with an interesting skeleton was isolated[4] from the oil of costus root (*Saussurea lappa* Clarke) and formulated as (*E*)-6,10-dimethyl-9-methylene-undec-5-en-2-one (I) on the basis of spectroscopic data. Literature[5] records a few syntheses of I. The present work represents a short and stereoselective synthesis of I via regioselective alkylation of α-metallo-N,N-dimethylhydrazone as shown in Scheme 1.

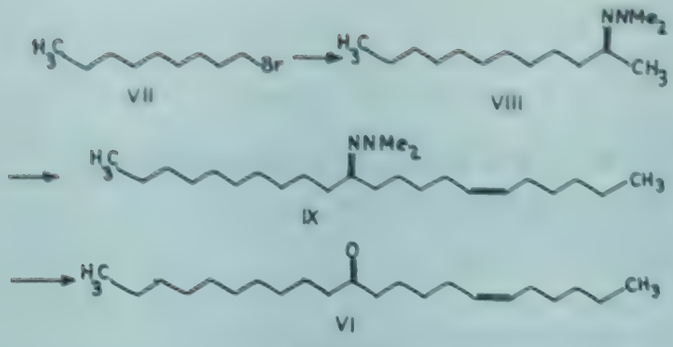
The alcohol[6] (II) was transformed into the bromide[7] (III) with LiBr via its tosylate in dry ether. Alkylation[8] of α-lithiomethyl isopropyl ketone dimethylhydrazone with bromide (III) in THF at -78° afforded IV in 84% yield. Hydrolysis of IV with $Cu(OAc)_2.H_2O$ in THF resulted in the formation of V in 52% yield after chromatography over neutral alumina. Base-catalysed (NaH/DMSO) Wittig reaction[9] of V with methyltriphenylphosphonium iodide followed by treatment with *p*-toluenesulphonic acid gave I as an oil (71.4%) after careful chromatography over silica gel. The spectral features (IR,PMR) of I agreed with those reported in literature.

A sex pheromone of Douglas firtussock (*Orgyia pseudotsugata*) was isolated by Ousset *et al.*[10] recently in low yield and its structure (VI) was arrived at on the basis of spectral data and confirmed by synthesis. The sequence of reactions leading to VI is outlined in Scheme 2.

Alkylation[8] of α-lithioacetone dimethylhydrazone with nonyl bromide (VII) in THF at -78° afforded VIII in 83.74%. Compound (VIII) was again metallatd with LDA (freshly prepared from diisopropylamine and 1.6 *N* *n*-BuLi) in THF at -78° and subsequent treatment with 1-bromo-4(*Z*)-decene[11] at -78° gave IX in 88.4% yield. Dimethylhydrazone (IX) on hydrolysis[2] with aq. sodium periodate at *p*H 7 and 20-25° using meth-



SCHEME 1



SCHEME 2

anol as cosolvent resulted in the formation of VI in 96% yield after column chromatography over neutral alumina. IR and PMR spectra of VI were in agreement with those reported in the literature.

Experimental Procedure

Boiling points reported are uncorrected. Pet. ether refers to the fraction, b.p. 60-80°. All organic extracts were dried over anhydrous sodium sulphate. Purity of all analytic samples was checked by TLC. IR spectra (thin films, ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer 337 instrument and 90 MHz PMR spectra on a Varian EM-390 instrument using TMS as an internal reference (chemical shifts in δ-scale).

6,6-*Ethylenedioxy*-1-*bromo*-2-*methyl*-2-(*E*)-*heptene* (*III*)

To a mixture containing the alcohol (II, 0.5 g, 2.68 mmol), dry HMPA (0.95 ml), dry ether (2.7 ml) and a crystal of triphenylmethane and cooled to 0°C was added with stirring *n*-Buli (1.75 ml of 1.55 *N*) in hexane. When the red colour persisted *p*-toluenesulphonyl chloride (540 mg, 2.8 mmol) in dry ether (2.7 ml) was added with stirring and the reaction mixture further stirred for 15 min. To this was added lithium bromide (235 mg, 2.7 mmol) at 0° with stirring. Stirring was continued for 3 hr at room temperature. The reaction mixture poured into ice-water, extracted with ether and dried. Evaporation of solvent gave III (0.548 g, 82%) which was used as such in the next operation. Its IR spectrum did not show any absorption in the hydroxyl region; PMR(CCl_4): 5.63(*t*,1H,C_3-H), 4.03 (*s*,2H, methylene at C-1), 3.96 (*s*, 4H, ethylenedioxy protons), 2.6-2.33 (*m*, 4H, methylenes at C-4, C-5), 1.77 (*s*, 3H,CH_3, at C-2), 1.3 (*s*, 3H, CH_3 at C-6).

2,2(1,2-*Ethanediyldioxy*)-6,10-*dimethyl*-5(*E*)-*undecen*-9-*one N,N-dimethylhydrazone* (*IV*)

To a solution of methyl isopropyl ketone dimethylhydrazone (1.1 g, 8.5 mmol) in THF (15 ml) at -78° under nitrogen atmosphere, was added *n*-Buli (5.5 ml of 1.6 *N*) in hexane followed by HMPA (4.5 ml) after 15 min. Stirring was continued for 30 min more and to this was added III (1.86 g, 7.46 mmol) in THF (15 ml) at -78° dropwise and allowed to warm to room temperature and kept overnight. Methanol (1 ml) was added and the solvent removed *in vacuo*. The residue was dissolved in water, extracted with ether and dried. Removal of solvent followed by column chromatography over neutral alumina gave pure IV (1.86 g, 84%); IR: 1650, 1050, 1200, 1415; PMR (CCl_4): 5.1 (*t*, 1H, proton at C-7), 3.9 (*s*, 4H, ethylenedioxy protons), 2.6-2.33 (*m*, 9H, methylene protons at C-4, C-5, C-8, C-9 and C_2-H), 1.83 (*s*, 3H, CH_3 at C-6), 1.27 (*s*, 3H, -CH_3 at C-10), 1.1 (*d*, 6H, *gem*-dimethyl protons), (Found: C, 68.8; H, 10.7. $C_{17}H_{32}O_2N_2$ requires C, 68.9; H, 10.9%).

2,2-(1,2-*Ethanediyldioxy*)-6,10-*dimethyl*-5(*E*)-*undecen*-9-*one* (*V*)

Hydrazone (IV, 1.5 g, 5.06 mmol) in THF (40 ml) was added to a solution of $Cu(OAc)_2.H_2O$ (3.2 g, 16 mmol) in water (60 ml). After 40 min, most of the THF was evaporated and the solution was diluted with 1.5 *M* aq.NH_4Cl (100 ml), the *p*H of the solution adjusted to 8 by the addition of 27% aq. NH_4OH, extracted with dichloromethane, the organic extract washed with 10% aq. H_3PO_4, saturated aq. $NaHCO_3$ and dried. Solvent evaporation followed by column chromatography (silica gel; pet. ether) afforded V (0.67 g, 52%); IR: 1715, 1150; PMR (CCl_4): 5.2 (*t*, 1H, proton at C-7), 4.0 (*s*, 4H, ethylenedioxy protons), 2.74-1.9 (*m*, 9H, methylene protons at C-4, C-5, C-8, C-9 and C_2-H); 1.66 (*s*, 3H; CH_3 at C-3), 1.3 (*s*, 3H, CH_3 at C-10), 1.2 (*d*, 6H, *gem*-dimethyls) (Found: C, 70.7; H, 10.1. $C_{15}H_{26}O_3$ requires C, 70.9; H, 10.23%).

6,10-*Dimethyl*-9-*methylene*-5(*E*)-*undecen*-2-*one* (*I*)

To sodium hydride (50% dispersion, 125 mg, 2.6 mmol) prewashed with hexane, was added dimethyl sulphoxide (5 ml) under N_2 atmosphere and heated at 75° for 45 min. The resulting solution was cooled and methyltriphenylphosphonium iodide (0.935 g, 2.60 mmol) in dimethyl sulphoxide (5 ml) was added. The resulting dark red solution was stirred for 15 min at room temperature and V (530 mg, 2.54 mmol) in DMSO (2 ml) was added. The mixture was stirred at 60° for 3 hr, quenched with water, extracted with pet. ether (3 × 25 ml), dried and solvent evaporated. The resi-

due was taken in acetone (20 ml) containing *p*-toluenesulphonic acid (100 mg) and stirred for 5 hr, poured into water (10 ml), extracted with pentane, washed with brine and dried. Evaporation of the solvent followed by column chromatography (silica gel; benzene/hexane) to give I as pure oil (0.31 g, 71.4%); IR: 1700, 1650, 1625; PMR(CCl_4): 5.2 (*t*, 1H, proton at C-7), 4.71 (*bs*, 2H, exomethylene protons), 2.7-2.0 (*m*, 9H, methylene protons at C-4, C-5, C-8, at C-9 and C_2-H), 1.9 (*s*, 3H, -CH_3 at C-10), 1.66 (*s*, 3H, -CH_3 at C-6), 1.05 (*d*, 6H, $J=7$ Hz, *gem*-dimethyls) (Found: C, 82.4; H, 10.3. $C_{14}H_{24}O$ requires C, 82.5; H, 10.5%).

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Enantioselective Synthesis of (*R*)-(+)-5-Hexadecanolide, the Pheromone of Queen of Oriental Hornet, *Vespa orientalis* Linn

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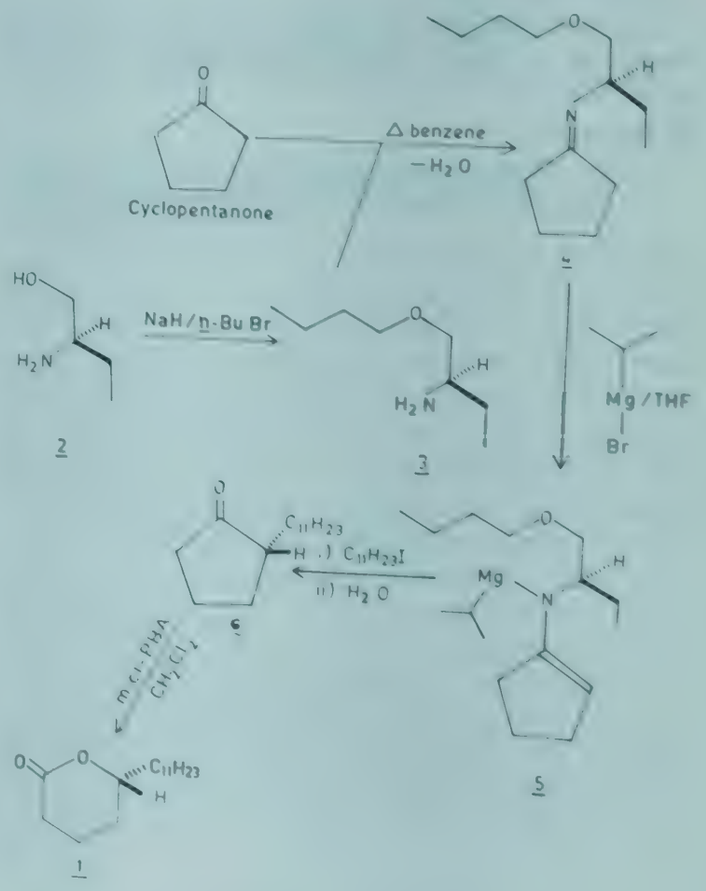
An enantioselective synthesis of (*R*)-(+)-5-hexadecanolide (**1**) using cyclopentanone, and (*R*)-2-aminobutyl-*n*-undecyl iodide (as electrophile) is reported.

The oriental hornet, *Vespa orientalis* Linn, is a social insect distributed throughout eastern tropical and subtropical countries of the world. The insects form annual colonies reigned over by a queen. These insects are one of the most serious enemies of honey bees, and also attack various summer fruits.

Ikan *et al.*[1] reported the isolation and structure elucidation of the pheromone, (*R*)-(+)-5-hexadecanolide (**1**) which was obtained from head of queen bees and was responsible for some aspects of social behaviour of the hornet.

The synthesis of the racemic **1** has been reported[2,3]. Coke and Richon[4] reported for the first time the synthesis of optically active **1**, wherein the classical optical resolution procedure was adopted. Pirkle and Adams[5] used HPLC technique to resolve (~60% optical purity) the racemic pheromone. Since then many reports[6-16] have appeared for the stereospecific synthesis of **1**.

Since most of the reported methods of synthesis involved optical resolution, or complex chiral-specific routes, we considered an approach involving addition of undecyl moiety to chiral cyclopentanoneenamine (**4**), followed by Baeyer-Villiger oxidation of the resulting alkylcyclopentanone to yield the desired lactone. Thus (*R*)-2-amino-*n*-butanol (**2**) (AR, Aldrich, 83% optical purity) was converted[17] into (R)-2-aminobutyl *n*-butyl ether (**3**) by alkylation with *n*-butyl bromide in the presence of sodium hydride in 80% yield. Compound (**3**) in benzene was refluxed with cyclopentanone and water was removed azeotropically to yield the required enamine (**4**). Earlier, Whitesell and Whitesell reported[17] an assymetric alkylation of cyclohexanone using the same amino ether (**3**) where a suitably situated ether oxygen underwent intramolecular solvation of the metal ion which inhibited rotation around the single bond resulting in stereospecific addition to the double bond. This procedure worked very satisfactorily in our hands and treatment of a solution of **4** in THF with



isopropylmagnesium bromide under reflux and N_2 atmosphere gave the complex (**5**) which was cooled to −78°C and treated *in situ* with undecyl iodide (prepared earlier from lauric acid by treatment with lead tetraacetate, UV irradiation and I_2) to give 2-undecylcyclopentanone (**6**) in 80% yield as a colourless viscous liquid. The ketone (**6**) on treatment with *m*-chloroperbenzoic acid (Baeyer-Villiger oxidation) in methylene chloride at 0° followed by stirring at ambient temperature for 24 hr gave the pheromone (**1**) in 90% yield, as a white solid, m.p. 29-30°C, $[\alpha]_D^{25}$ + 20.8 (THF) (lit.[1] m.p. 37°; $[\alpha]_D^{21}$ + 40.8°). Its spectral data (IR, PMR) compared well with those of (*R*)-(+)-5-hexadecanolide. The optical purity of the synthetic

compound was better than 50% (lit.[8] $[\alpha]_D^{20}$ + 39.8°, THF). The enantiomeric excess of the synthetic product was better than 62% (based on the corrected rotation of (*R*)-2-amino-1-butanol).

Experimental Procedure

Melting points were taken on a Kofler hot stage and are uncorrected. Optical rotations were measured in THF at ambient temperature (25-27°). IR spectra were recorded either on thin films or in $CHCl_3$ on a Perkin-Elmer spectrophotometer and PMR spectra in $CDCl_3$ on a Bruker 80 MHz spectrometer, chemical shifts in δ-scale downfield ppm and TMS as internal reference.

2-Aminobutyl n-butyl ether (**3**)

2-Amino-1-butanol (**2**) (22 g) was alkylated with butyl bromide (23 g) according to the reported procedure[17] when **3** was obtained as colourless liquid (10.2 g), $[\alpha]_D^{27} = -7.17°$ (neat) (Found: N, 9.7%. Calc for $C_8H_{19}ON$:N, 9.6%).

Undecyl iodide (9.8 g) was prepared according to the reported procedure[18] using lauric acid (8 g), lead tetraacetate (18 g) and iodine crystals (5.3 g) and purified by column chromatography on silica gel as a colourless liquid, b.p. 148-50°/13 mm.

(*R*)-2-*Undecacyclopentanone* (**6**)

A solution of cyclopentanone (1.7 g) and **3** (3 g) in benzene (50 ml) was refluxed for 12 hr under N_2 atmosphere using a Dean-Stark water separator. Benzene was removed *in vacuo*, the resulting enamine (**4**) dissolved in dry THF (5 ml) and added dropwise under N_2 atmosphere to a refluxing solution of isopropylmagnesium bromide [prepared from isopropyl bromide (2.7 g), magnesium turnings (0.6 g) and dry THF (15 ml)]. The solution was refluxed for 2 hr to yield the complex. The complex (**5**) without isolation was cooled to −78°C and undecyl iodide (7.7 g) in dry THF (5 ml) was added to it dropwise with stirring during 15 min. The reaction mixture was kept at −78° for further 15 min, warmed slowly to 0° and 2*N*HCl (11 ml) added to it. After 15 min, the reaction mixture was worked-up by extracting it with pet. ether (40-60°), followed by washing the organic layer with dil. aq. oxalic acid, 5% aq $NaHCO_3$ and brine. The solvent was removed under reduced pressure to afford crude **6** (3.78 g ~80%), which was purified by column chromatography on silica gel, elution with 30% $CHCl_3$ in hexane gave TLC single, a colourless liquid, b.p. 137-40°/15 mm (1.87 g); IR (neat):1745 (>C=O), 1465, 1160, 930 cm^{-1}; $[\alpha]_D^{25}$ +6.58°; PMR:0.9 (3H, *t*, *J*=6 Hz), 1.27 (~22 H, *s*). 1-77-2.1 (3H, *m*, $-CH_2-CO-CH-R$) (Found: C, 80.1; H, 12.7 Calc. for $C_{16}H_{30}O$: C, 80.6; H, 12.7%).

Baeyer-Villiger oxidation of **6**:*Formation of* (*R*)-(+)-5-*hexadecanolide* (**1**)

To the ketone (**6**, 0.2 g) in methylene chloride (15 ml) was added *m*-chloroperbenzoic acid (160 mg, 1.1 equiv) in CH_2Cl_2 (10 ml) at 0°. The reaction mixture was kept at room temperature for 24 hr. On working-up as usual, a pale coloured gum (0.15 g) single spot on TLC (~70%) was obtained. It crystallised from hexane to afford **1** as a while solid, m.p. 29-30°C (lit.[8] 38°), $[\alpha]_D^{25}$ + 20.8° (THF) (Found: C, 75.1; H, 11.6 Calc for $C_{16}H_{30}O_2$: C, 75.5; H, 11.9%); IR ($CHCl_3$):1745 (−CO), 1235, 1170, 1120 cm^{-1}; PMR: 0.89 (3H, *t*, *J*=6Hz, terminal methyl), 1.27 (~18 H, *s*, methylenes), 1.60-2.10 (4H, *m*, $-CO-O-\underset{\displaystyle CH_2}{\overset{\displaystyle |}{C}}-CH_2-$), 2.50(2H, *bs*, $-CH_2-COO-R$), 4.11 (1 H, *m*, $-O-CH-$).

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Stoichiometric Hydroboration-Oxidation Reaction of Monocyclic Monoterpenoids: A Mechanistic Approach

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The Stoichiometric studies on hydroboration-oxidation reactions of (−)-carvone have been carried out to gain an insight into the mechanism of formation of unusual products 2-oxo-*p*-menth-9-ols (IVb,c), *p*-menth-2,9-diols (Xa,b) and *p*-menth-1-en-9-ol (VII). Based on high resolution PMR spectral data, the stereochemistry of IVb,c and Xa,b has been deduced. Similar studies have been extended to (+)-dihydrocarvone and (−)-carveol.

Hydroboration-oxidation reaction bears an eloquent testimony to its synthetic potential since it generates an interesting array of reactions where most of organic functional groups are reduced selectively. Perhaps an illuminating example in this context is the hydroboration-oxidation reaction of monocyclic monoterpenoid, (+)-carvone[1] (I). The reaction needs special mention since it gave the unusual products 2-oxo-*p*-menth-9-ol and *p*-menth-2,9-diol (Chart 1; IVa and Va,b) instead of the inevitable *p*-menth-2,6,9-triol, in the presence of excess of E I_3 − THF. However, the findings reported therein are of very preliminary nature and no rationale was provided to account for the formation of these products. It therefore demanded radical approach to gain an insight into the formation of the products IVa and Va,b. The results of the stoichiometric studies on this reaction employing (−)-carvone are reported in this paper.

The total conversion of (−)-carvone into the products was achieved by treating it with 1.0 and 1.5 mol equiv of BH_3 − THF followed by oxidation ($NaOH/H_2O_2$). Treatment with 0.5 mol equiv of BH_3 − THF effected 50% conversion of (−)-carvone implying that this molar quantity was not enough. The results of GLC analysis (OV-101, 180°) of the crude products are given in Table 1.

The results of stoichiometric hydroboration-oxidation reactions, shown in Table 1, suggest that 1.0 nd 1.5 mol equiv of BH_3 − THF are the minimum requirements for the total conversion of carvone into a mixture of products in which compounds IVb, c and Xa,b† are the major products

Table 1—GLC Analysis of the Products Resulting from (−)-Carvone and 1.0 and 1.5 Mol Equiv. of BH_3 − THF

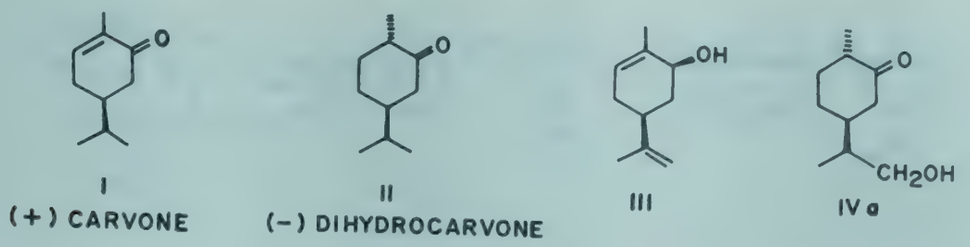
Mol. equiv of BH_3 − THF	Product*	Yield (%)
1.0	IVb,c	45.2
	Xa,b	15.3
	VII	15.5
	Triol	7.0
	High boiling viscous liquid	10.0
1.5	Xa,b	56.8
	IVb,c	Traces
	VII	13.3
	High boiling viscous liquid	24

*Products IV, VII and X gave satisfactory C and H analyses.

respectively. Several mechanistic possibilities are tenable to depict the formation of these products in the absence of stoichiometric results. However, we invoke a possible intermediate XI (Scheme 1) which subsequently gives IVb,c. The reaction is initiated by 1,4-addition of BH_3 to α,β-unsaturated carbonyl group.

Two mechanistic possibilities emerge out to account for the formation of Xa,b as a result of stoichiometric studies. In one of the routes 1,2-addition of BH_3 to α,β-unsaturated carbonyl group followed by hydroboation of exomethylenic double bond of (−)-carvone results in the formation of an oxonium ion XII (Scheme 2a). The uptake of an hydride ion by this intermediate is a favourable step since it involves neutralisation of the charge giving rise to an important organoborane intermediate XIII which on oxidation yields VII

† Attempts to separate the diastereoisomers IVb,c and Xa,b by column chromatography and preparative GC were unsuccessful.

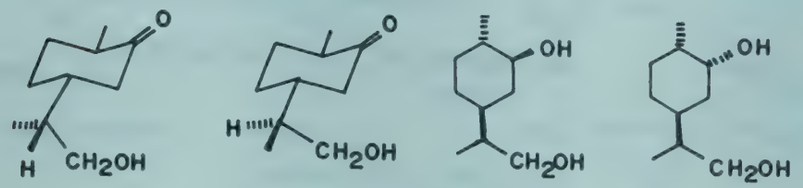


I (+) CARVONE

II (−) DIHYDROCARVONE

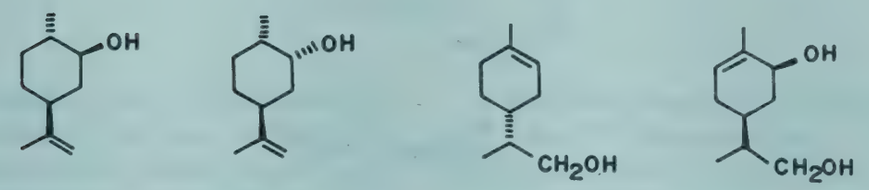
III

IV a



IV b,c

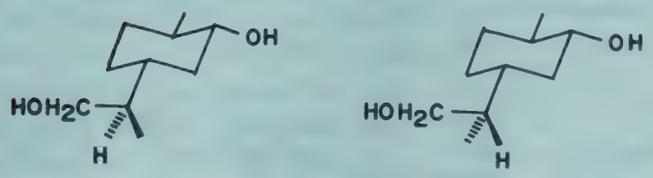
V a,b



VI a,b

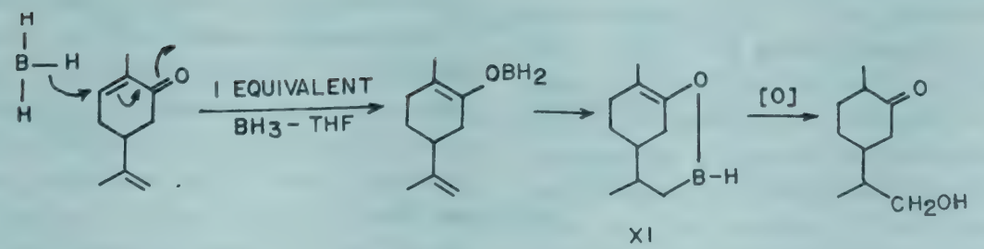
VII

VIII



X a,b

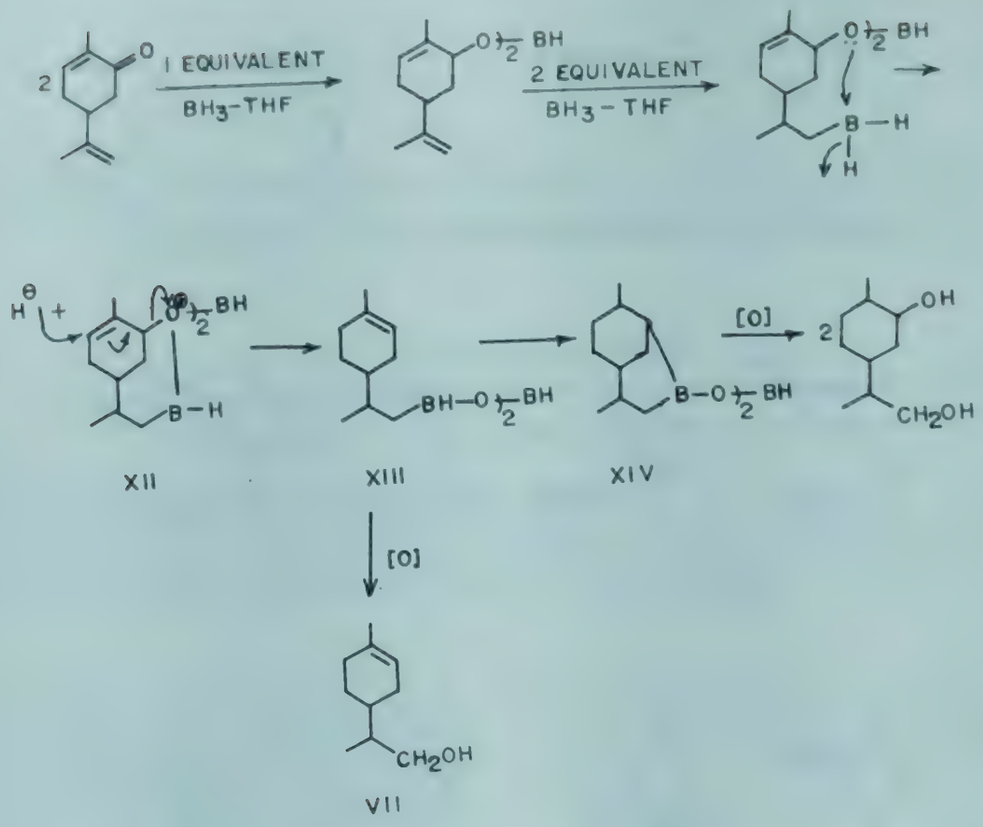
CHART 1



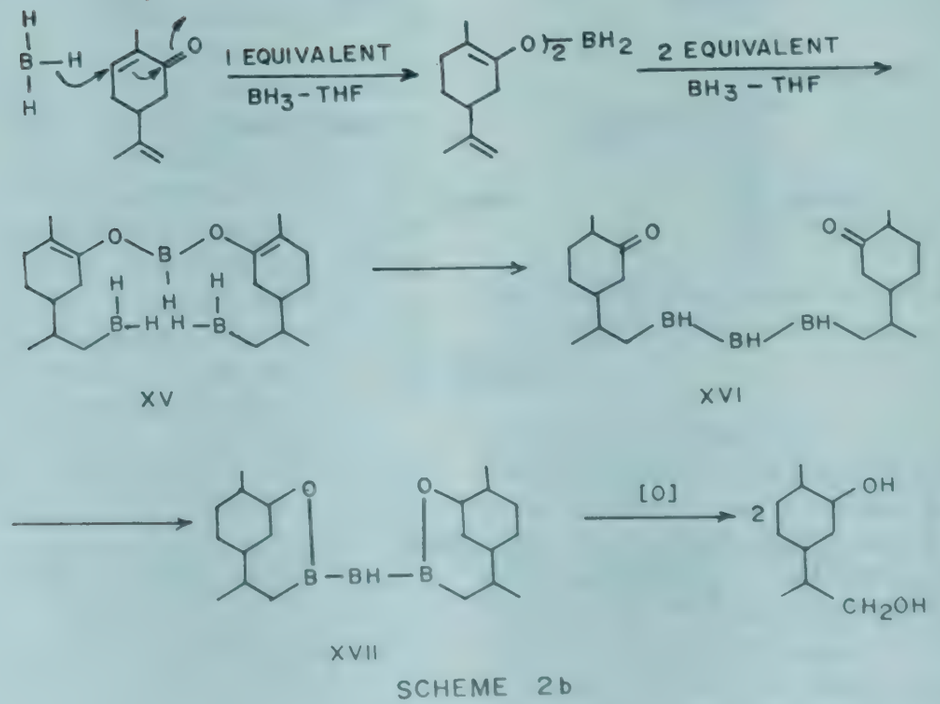
XI

SCHEME 1

The internal hydroboration of XIII furnishes XIV which on oxidation yields Xa,b. In the second route, 1,4-addition of BH_3 to α,β-unsaturated carbonyl group of (−)-carvone followed by hydroboration of exomethylenic double bond provides an organoborane XV (Scheme 2b) which immediately rearranges to XVI with the concomitant formation of B−B bond. The internal hydride reduction of carbonyl group in XVI followed by oxidation gives Xa,b. The major disad-



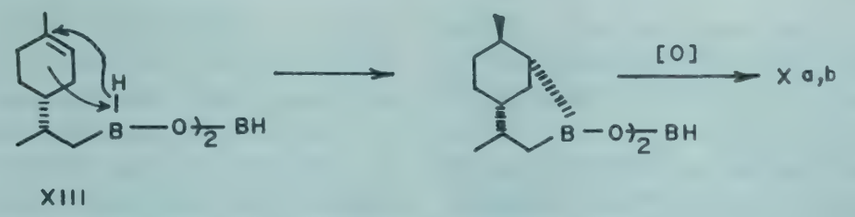
SCHEME 2a



SCHEME 2b

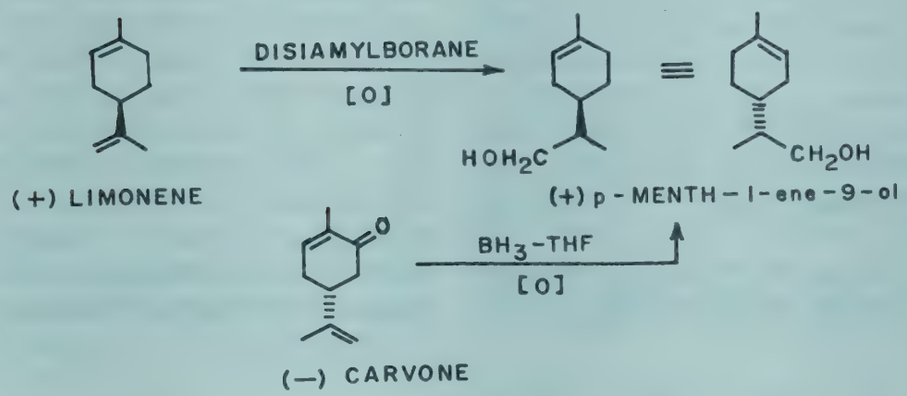
vantage of this mechanism is that it is unable to explain the formation of *p*-menth-1-en-9-ol (VII).

GLC analysis of IV indicated it to be a single compound with 98% purity (OV-101, 180°). Theoretically, four stereoisomers of IV are possible. However, its formation via enol-form (Scheme 1) necessitates it to take up the most stable conformation where C_1-methyl and isopropyl groups are *trans* to each other. Its PMR spectrum (270 Mhz) in $CDCl_3$ exhibited a closely spaced four line multiplet at 0.91 suggesting *R*- and *S*-configurations for C-8 in IVb, c and also implying that addition of boron-hydrogen linkage to the exomethylenic double bond takes place from both α and β sides. The nonstereoselectivity at C-8 is difficult to realise with the intermediate XI



XIII

SCHEME 3



SCHEME 4

(Scheme 1). Alternatively, the enolborane intermediate, the precursor of XI, may undergo hydroboration of exomethylenic double bond in the presence of another molecule of enolborane accomplishing the nonstereoselectivity at C-8.

p-Menth-2,9-diol(X)‡ was found to be a mixture of two isomers in the ratio of 87:13 as determined by GLC analysis (OV−101, 180°, RT 2.98 and 3.29). The stereoselectivity achieved at C-1 and C-2 in Xa,b demands BH_3 to approach the trisubstituted double bond in XIII from the side of isopropyl group (α-side; Scheme 3).

Similarly, the organoborane XV rearranges to XVI (Scheme 2b) via its enol-form, implying a *trans* relation between C_1-methyl and isopropyl groups in XVI. Further, the initial bond formation between oxygen of the carbonyl group and boron in XVI results in a stereoselective reduction of carbonyl group, forming exclusively α-equatorial hydroxyl group in Xa,b. However, it is imperative from PMR spectrum (270 MHz) of Xa,b that the selectivity is not observed at C-8 and C_8-methyl hydrogens appear as a closely spaced four line multiplet at δ 0.89 implying that C-8 has *R*- and *S*-configurations. The C_2-H in Xa,b appeared at δ 31.5 as triple doublet with coupling constants 4.5 and 8.0 Hz supporting α-orientation for C_2-OH group. Therefore, *p*-menth-2,9-diol is a mixture of two stereoisomers Xa and Xb.

‡The diol mixture obtained from 1.0 mol equiv of $THF-BH_3$ contained the two isomers in 55:45 ratio

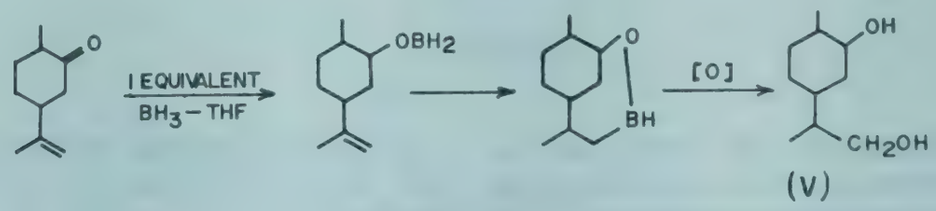
It has been reported by Schulte-Elte and Ohloff[2] that (+)-limonene $[\alpha]_D+125°$, gives (+)-*p*-menth-1-en-9-ol ($[\alpha]_D+87°$) on selective hydroboration-oxidation in the presence of disiamylborane (Scheme 4). (−)-Carvone could give the same monol on hydroboration-oxidation reaction in the presence of BH_3-THF provided there is a shift of double bond from $\Delta^{1,6}$ to $\Delta^{1,2}$ (Scheme 2a; XII → XIII). The isolation of *p*-menth-1-en-9-ol (VII), $[\alpha]_D+81°$, provided substantial evidence in favour of the mechanism shown in Scheme 2a.

The unusual formation of 2-oxo-*p*-menth-9-ol (IVa) and *p*-menth-2,9-diol (Va,b) prompted Kulkarni *et al.*[3] to extend their studies to other derivatives of carvone. They reported the formation of a mixture of *cis*- and *trans*-dihydrocarveols (Chart 1; VIa,b) on hydroboration-oxidation of (−)-dihydrocarvone (II) in the presence of excess of BH_3-THF. It is quite interesting to note that the exomethylenic double bond in II remained unaffected, for which no explanation was provided. Apparently, all is not well with these findings as the formation of *p*-menth-2,9-diol is an inevitable event of this reaction. This, therefore, required reexamination to overcome ambiguities if there were any. They also reported[3] that (+)-carveol (Chart 1, III), in the presence of excess of BH_3-THF gives mainly *p*-menth-6-ene-2,9-diol (VIII) implying selective hydroboration of the exomethylenic double bond. In fact, the excess of diborane should lead to *p*-menth-2,6,9-triol. These reactions were reinvestigated and we report herein our results.

Treatment of (−)-dihydrocarvone with 1.0 mol equiv of BH_3-THF gave 15% unreacted dihydrocarvone along with 85% of *p*-menth-2,9-diol (V). Therefore, we rule out the possibility of formation of dihydrocarveol as the only product of hydroboration-oxidation reaction. The stoichiometric results are in accordance with the mechanism depicting the formation of *p*-menth-2,9-diol (Scheme 5). Alternatively initial hydroboration of the exo-double bond followed by stereoselective internal hydroboration of the keto function explains the isomerism at C-8. The GLC analysis of *p*-menth-2,9-diol thus obtained has been compared with that obtained from (−)-carvone in Table 2.

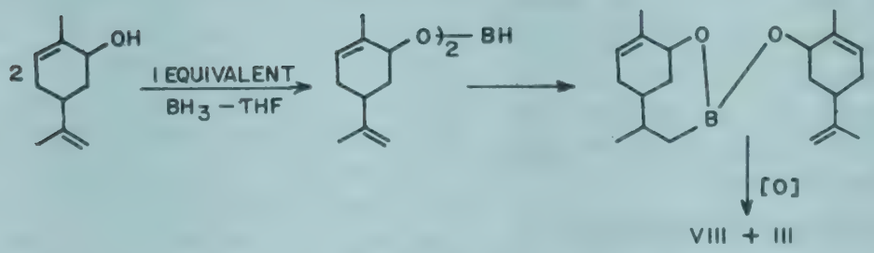
Therefore one is tempted to conclude that the diol isomers Xa and Xb obtained from (−)-carvone are identical with those obtained from (+)-dihydrocarvone. However, high resolution PMR spectrum of the mixture of diols obtained from (+)-dihydrocarvone (see experimental) indicated the presence of four stereoisomers as shown in Chart 2. The formation of such a mixture of diol isomers was very much expected as the starting compound (+)-dihydrocarvone was a mixture of *trans* (83%) and *cis* (17%) isomers.

(−)-Carveol gave *p*-menth-6-en-2,9-diol and the unreacted carveol in 46.5 and 52% yields respectively in the presence of 0.5 mol equiv of BH_3-THF; *p*-menth-2,6,9-triol was formed in a trace amount. The mechanism of formation of *p*-menth-6-en-2,9-diol is depicted in Scheme 6 which is in accordance with the stoichiometric studies. GLC analysis indicated it to be a single



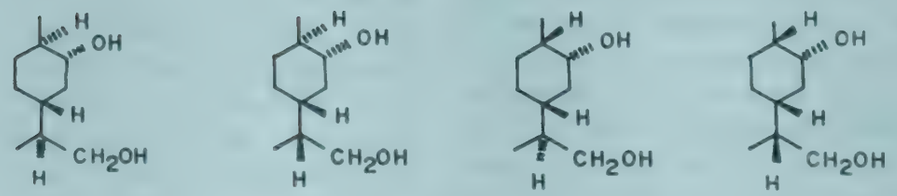
(V)

SCHEME 5



VIII + III

SCHEME 6



C_1 − METHYL HYDROGENS APPEAR AT 1·06 PPM AS DOUBLET

C_1 − METHYL HYDROGENS APPEAR AT 0·946 PPM AS DOUBLET

C_8 − METHYL HYDROGENS APPEAR AS FOUR LINES CENTERED AT δ 0·895 PPM

STEREOISOMERS OF P-MENTH-2,9-DIOL (V) OBTAINED FROM (+)-DIHYDROCARVONE

CHART 2

Table 2—GLC Analysis of *p*-Menth-2,9-diol Samples Obtained from (−)-Carvone and (+)-Dihydrocarvone by Treatment with BH_3 − THF

(−)-Carvone (1.5 mol equiv. BH_3 − THF)				(+)-Dihydrocarvone (1.0 mol equiv. BH_3 − THF)			
RT	Temp °C	Product		RT	Temp °C	Product	
7.02	150	Diol	Xa,Xb	7.13	150	Diol	V
8.17	150	Diol		8.10	150	Diol	
2.98	180	Diol	Xa,b	2.99	180	Diol	V
3.29	180	Diol		3.34	180	Diol	

compound with 99% purity (OV−101, RT 3.5, 180°), m.p. 110°, $[\alpha]_D$ −23.5°. Its PMR spectrum exhibited a broad signal at δ 4.15 indicating α-orientation for C_2 − OH.

Experimental Procedure

Borane-tetrahydrofuran (BH_3 − THF) solution approximately 2*M* was prepared according to the standard procedure of Brown *et al.*[4], by the addition of $BF_3 \cdot O(Et)_2$ to $NaBH_4$ in diglyme. Its molarity was determined from the amount of hydrogen liberated by hydrolysis of BH_3 − THF solution with 1:1 water-glycerol, as per the standard technique utilized for the estimation of hydride molarity[5].

Hydroboration-oxidation of monocyclic monoterpenoids: General Procedure

It was achieved by the addition of stoichiometric amounts of BH_3 − THF with stirring to the monoterpenoid in THF at 0° under nitrogen blanket, over a period of 20-30 min, and the reaction mixture stirred at room temperature for 1.5-2.0 hr. Oxidation of the organoborane thus formed was carried out without isolation with 30% hydrogen peroxide and 3*N* NaOH.

Stoichiometric hydroboration-oxidation of (−)-carvone (1:1 *molar ratio*)

A solution of BH_3 − THF (44 ml, 0.074 *M* BH_3, 10% excess) was added dropwise to a solution of (−)-carvone ($[\alpha]_D$ − 56°) (10.0 g, 0.066 *M*) in THF (30 ml) cooled in ice-bath, with stirring under nitrogen atmosphere. The oxidation of the organoborane thus obtained was carried out by adding 3*N* NaOH and 30% H_2O_2 simultaneously. Usual work-up gave a crude product (8.8 g) which on column chromatography over silica gel provided compounds IVb,c; Xa,b and VII in pure state.

The reaction of (−) carvone was similarly carried out with 1.5 and 0.5 mol equiv of BH_3:THF.

The characterization data of the products, thus obtained, are given below:

2-*Oxo-p-menth*-9-*ol* (*IVb,c*):b.p. 140-41°/1 mm, $[\alpha]_D$-15°; semicarbazone: m.p. 150°; IR(liquid) spectrum matched with that reported in literature[1]; PMR (270 MHz, $CDCl_3$): 0.91 (four lines 3H, C_8 − Me), 1.0 (*d*, *J*=7 Hz, 3H, C_1 − Me), 3.53 (*m*, 2H, CH_2OH).

p-Menth-2,9-*diol* (*Xa,b*): It was obtained by treating (−)-carvone with 1.5 mol equiv BH_3 − THF b.p. 145-48°/1 mm; IR spectrum matched with that reported in literature; PMR (270 MHz, $CDCl_3$): 0.895 (four lines, 3H, C_8 − Me), 1.0 (*d*, *J*=7 Hz, 3H, C_1 − Me), 3.15 (*dt*, J=4.5 and 8 Hz, 1H, CHOH) 3.5 (*m*, 2H, CH_2OH).

p-Menth-1-*en*-9-*ol* (*VII*): b.p. 54-56°/1 mm; $[\alpha]_D$ + 81°; IR(liquid): 3340 (OH), 1650 (>C=CH−), 1040 (C−O), 800 cm^{-1} (>C=CH-bending); PMR (90 MHz, $CDCl_3$); 0.95 (*d*, *J*=7 Hz, 3H, C_8 − Me), 1.65 (*s*, 3H, $C=\underset{|}{C}-CH_3$), 3.55 (*m*, 2H, CH_2OH), 5.37 (*bs*, 1H, −CH=C<).

Stoichiometric hydroboration-oxidation of (+)-dihydrocarvone

A solution of BH_3 − THF (40.0 ml, 0.074 *M*, 10% excess) was added dropwise to a solution of dihydrocarvone ($[\alpha]_D$ + 16.7°) (10.0 g, 0.066 *M*), obtained from (−)-carvone by reaction with $NaBH_4$ and pyridine[6] in THF (30 ml). The work-up as described for carvone gave the crude product (8.0 g) which on column chromatography over silica gel yielded *p*-menth-2,9-diol (Chart 2), b.p. 140-142°/1 mm; PMR (270 MHz, $CDCl_3$): 0.895 (four lines, 3H, C_8 − Me), 0.94 and 1.0 (*d*, *J*=6 Hz, 3H, C_1 − Me), 3.15 (*dt*, *J*=4.5 and 8 Hz, 1H, CHOH), 3.5 (*m*, 2H, CH_2OH).

Stoichiometric hydroboration-oxidation of (−)-carveol

A solution of BH_3 − THF (20. 0 ml, 0.031 *M*) was added dropwise to a solution of (−)-carveol ($[\alpha]_D$ − 41.6°) (9.59, 0.056 *M*) in THF (20 ml). The usual work-up gave a crude product (7.6 g) which on column chromatography over silica gel furnished *p*-menth-6-en-2,9-diol (VIII) as a colourless crystalline solid, m.p. 110°, $[\alpha]_D$ − 23.5°; IR(nujol): 3320 (OH), 1040 (C−O) and 780 cm^{-1} (trisubstituted C=C); PMR (90 MHz, $CDCl_3$): 0.95 (*d*,*J*=7 Hz, 3H, C_8 − Me), 1.75 (*s*, 3H, $>C=\underset{|}{C}-CH_3$), 3.56 (*m*, 2H, CH_2OH), 4.15 (*bs*, $W_{1/2}$ = 18 Hz, 1H, CHOH).

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Reaction of Acetic Anhydride/Zinc Chloride Reagent with Phenols : Improved Yields of Hydroxyacetophenones

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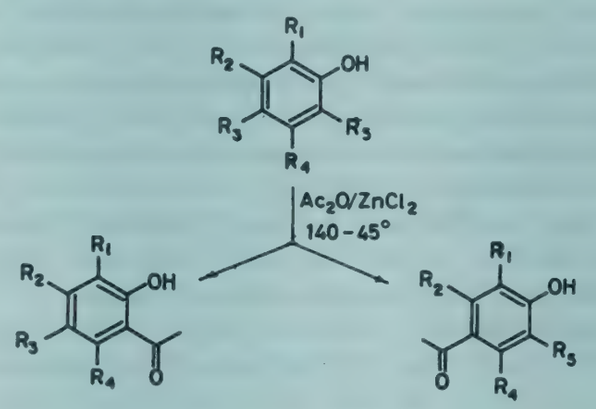
Acetic anhydride/zinc chloride has been found to be a better acylating system for phenol and polyphenols resulting in improved yields of the respective hydroxyacetophenones. The phenols used are phenol, resorcinol, hydroquinone, catechol, phloroglucinol and pyrogallol. With resorcinol the isomeric diacetyl derivatives are formed in excellent yields in a single step, while catechol and hydroquinone give only mono acetyl derivatives like simple phenol. Pyrogallol gives a monoacetyl derivative while phloroglucinol gives both mono and diacetyl derivatives but not triacetyl derivatives.

Hydroxyacetophenones have been prepared by several methods[1-3] and efforts are still on in exploring newer reagents to achieve economically viable yields. Zinc chloride/acetic anhydride has been found to be a new Friedel-Crafts reagent in our laboratories[4,5] to give 5-acetyl-2,4-dihydroxyacetophenone(**1**) in a single step from resorcinol in excellent yield. While studying this reaction in greater detail, the effective use of the new acylating system has been tried on other phenolic substrates, viz. phenol, hydroquinone, catechol, phloroglucinol and pyrogallol.

The reaction of resorcinol (1 mol) with Ac_2O (2 mol) and $ZnCl_2$ (2 mol) yielded 5-acetyl-2,4-dihydroxyacetophenone (**1**, 90%), m.p. 178-79°, its isomer, 3-acetyl-2,4-dihydroxyacetophenone (**2**, 7%), m.p. 90° and 2,4-dihydroxyacetophenone (**3**, 2%), m.p. 144°. Several experiments have been carried out by varying the molar proportions of Ac_2O and $ZnCl_2$ as well. The use of 0.5 or 1 mol of Ac_2O resulted in the formation of **3** with no traces of **1** or **2**. A minimum of two mol of Ac_2O was needed for diacetylation, while use of higher molar proportions had little effect on the overall yield of the diacetyl compound. While one mol of $ZnCl_2$ was enough to complex with two mol of acetic anhydride[8], the use of two mol of $ZnCl_2$ was found necessary to bring out complete diacetylation.

Several reagents have been reported in literature[1a] for the acetylation of resorcinol with yields as high as 90%, but all these afforded only compound **3**. Balasubrahmanyan *et al.*[6] reported recently the formation of **1**, but only in 66% yield by the acetylation of resorcinol by acetyl chloride in the presence of $FeCl_3$. Acetic anhydride/zinc chloride thus proved to be a much better reagent to give **1** in nearly quantitative yield. Polyacetylation of a phenolic substrate in a single step is rather rare as the substrate becomes less reactive after the introduction of an electron withdrawing acetyl group.



(1) $R_1=R_4=H; R_2=OH; R_3=COCH_3$
(2) $R_3=R_4=H; R_2=OH; R_1=COCH_3$
(3) $R_1=R_3=R_4=H; R_2=OH$
(4) $R_1=R_2=R_3=R_4=H$
(5) $R_1=R_2=R_4=R_5=H$
(6) $R_1=R_2=R_4=H; R_3=OH$
(7) $R_2=R_4=R_5=H; R_1=OCOCH_3$
(8) $R_2=R_4=R_5=H; R_1=OH$
(9) $R_1=R_3=H; R_2=R_4=OH$
(10) $R_1=H; R_2=R_4=OH; R_3=COCH_3$
(11) $R_3=R_4=H; R_1=R_2=OH$

The effect of this reagent (Ac_2O-$ZnCl_2$) was also studied on mono-, di- and tri-hydric phenols. Acetylation of phenol (1 mol) with Ac_2O (1.25 mol) and $ZnCl_2$ (1.25 mol) afforded 2-hydroxyacetophenone (**4**, 36%) and 4-hydroxyacetophenone (**5**, 40%), m.p. 104-6°. The reaction of phenol with twice the molar proportions of Ac_2O and $ZnCl_2$ did not result in any appreciable increase in the yield of either of the acetophenones. Several reagent combinations have earlier been used for acylation of phenol with varying yields of 2- and 4-hydroxyacetophenones[1a]. The overall yield of acetophenone reported is as low as 2% with acetyl chloride-$BuSO_3H$, 95% with acetic acid-BF_3, 90% with acetyl chloride-$AlCl_3$, 85% with acetic acid-PPA, 81% with acetyl chloride-$TiCl_4$ and 71.5% with acetic anhydride-70% $HClO_4$. The use of $Ac_2O/ZnCl_2$ gave an overall yield of 76% comparable with the above reagents, while it proved certainly a better reagent than acetic

acid/$ZnCl_2$ (7%). Another interesting observation is the formation of 2-hydroxyacetophenone in greater proportion, while in most of the other cases, except in acetic anhydride-70% $HClO_4$[7], 4-hydroxyacetophenone is the major product.

The reaction of hydroquinone (1 mol) with Ac_2O (2 mol) and $ZnCl_2$ (2 mol) led to 2,5-dihydroxyacetophenone (**6**), m.p.200° in 76% yield. In this case also this reagent was found to be a better one than acetic acid/$ZnCl_2$ (20-25%)[1a].

Acetylation of catechol (1 mol) with Ac_2O (3 mol) and $ZnCl_2$ (3 mol) resulted in 3,4-dihydroxyacetophenone (**8**, 51%), m.p.116° along with 3-acetoxy-4-hydroxyacetophenone (**7**, 8%), m.p. 74-76°. Three mols of acetic anhydride were found necessary in this reaction, with lesser amounts resulting in poor yields. With other reagents the product formed was found to be only 3,4-dihydroxyacetophenone, except in one case where the formation of 2,3-dihydroxyacetophenone was reported in the presence of acetic anhydride-70% $HClO_4$ (ref. 7). It is noteworthy that $Ac_2O/ZnCl_2$ behaved differently from $Ac_2O/HClO_4$ in that the fomer effected *para*-acetylation. While the latter *ortho*-acetylation.

Phloroglucinol (1 mol) with Ac_2O (3 mol) and $ZnCl_2$ (3 mol) gave 2,4,6-trihydroxyacetophenone (**9**), m.p. 214-16° in 50% and 5-acetyl-2,4,6-trihydroxyacetophenone (**10**), m.p. 173° in 25% yields. Enhanced molar proportions of acetic anhydride and zinc chloride had no effect on the overall yield. Phloroglucinol like resorcinol forms an interesting reactive substrate with enhanced reactivity at *ortho* positions with respect to all the phenolic hydroxyls that might possibly result in a triacetyl derivative as well but no such drivative was formed.

Pyrogallol (1 mol) with Ac_2O (3 mol) and $ZnCl_2$ (3 mol) yielded 2,3,4-trihydroxyacetophenone (**11**), m.p. 171-73° in 53% yield and proved to be as good as acetic acid/$ZnCl_2$ with 52% yield. Enhanced molar proportions of Ac_2O and $ZnCl_2$ neither effected the yield of **11** nor brought about any polyacetylation.

The compounds obtained by the acetylation of phenol, resorcinol, hydroquinone, catechol, phloroglucinol and pyrogallol are listed in Table 1 along with their yields.

The essential reaction between zinc chloride and acetic anhydride may be represented as

$$2(CH_3CO)_2O + ZnCl_2 \rightarrow (CH_3CO)_2^{2+}[ZnCl_2(OCOCH_3)_2]^{2-} \quad \ldots(1)$$

The electronic configuration of $ZnCl_2$ is such that one mol of it generates two acetylium ions from two mols of acid anhydrides[8]. It was reported that $ZnCl_2$ as well as BF_3 form addition complexes with anhydrides and acylate aromatic compounds without displacement of halide from the Lewis acid[9]. Acylation of phenols may proceed either through electrophilic substitution of phenolic substrate or by the initial formation of an ester which undergoes Fries rearrangement subsequently. The above two processess are important and become competitive depending upon the phenolic substrates. Trace amounts of phenol acetates have been occasionally isolated along with hydroxy ketones. Satchell[10], while studying the acylation reactions of phenols with acid anhydrides in the presence of $SnCl_4$ reported the formation of phenolic esters only instead of hydroxyacetophenones.

The formation of 3-acetoxy-4-hydroxyacetophenone (**7**) noticed only with catechol, may support partly, but not unequivocally, the idea that phenols undergo acylation through the initial formation of esters. The possibility of direct acylation of a phenolic substrate can not be totally excluded as the reagents are known to acylate even the less reactive non-phenolic aromatic hydrocarbon substrates like methylpyrene[11].

It has been the general observation of several

Table 1—Products Formed in the Acylation of Phenol and Polyphenols

Sl No.	Phenolic Compound	Products	Yield (%)
1	Resorcinol	5-Acetyl-2,4-dihydroxyacetophenone (**1**)	90
		3-Acetyl-2,4-dihydroxyacetophenone (**2**)	7
		2,4-Dihydroxyacetophenone (**3**)	2
2	Phenol	2-Hydroxyacetophenone (**4**)	36
		4-Hydroxyacetophenone (**5**)	40
3	Hydroquinone	2,5-Dihydroxyacetophenone (**6**)	76
4	Catechol	3-Acetoxy-4-hydroxyacetophenone (**7**)	8
		3,4-Dihydroxyacetophenone (**8**)	51
5	Phloroglucinol	2,4,6-Trihydroxyacetophenone (**9**)	50
		5-Acetyl-2,4,6-trihydroxyacetophenone (**10**)	25
6	Pyrogallol	2,3,4-Trihydroxyacetophenone (**11**)	52

workers[8,10,12] that the rate of acylation reaction increases several folds when acetic anhydride is used instead of acetic acid. The difference might lie in the fact that the intermediate complex which is formed with acetic anhydride dissociates only by acquisition of a proton either from the phenol or from the nucleus, while when acetic acid is used as the acylation agent, the acylium cation may be too short-lived to be liberated and gets deactivated too early before effecting acylation.

Experimental Procedure

Phenol (b.p. 183°), resorcinol (b.p. 273°) and pyrogallol (b.p. 309°) were purified by double distillation under anhydrous condition, hydroquinone by recrystallisation from water (m.p. 170°), catechol by sublimation and phloroglucinol by heating at 120° for 2 hr. Acetic anhydride free from acetic acid was obtained by treating the laboratory grade acetic anhydride with calcium carbide followed by distillation[13]. Commercial grade zinc chloride sticks were freshly fused before use. A common experimental procedure was employed in all the reactions as given below.

General methoa for the preparation of hydroxyacetophenones

To a mixture of zinc chloride (one mol for each OH in the substrate) in dry acetic anhydride (one mol for each OH in the substrate), the dry phenolic compound (1 mol) was added quickly with stirring. The reaction mixture was slowly heated on a wire gauze and kept at 145-50° for 15 min. The resulting viscous solution was allowed to cool to room temperature and ice-cold aq. HCl (1 litre) was added to it with stirring. In the case of resorcinol and phloroglucinol an orange-red crystalline material separated out, while in the case of phenol, hydroquinone, catechol and pyrogallol a dark brown solution resulted which was extracted thrice with ether. The ether solution was washed with water, dried ($MgSO^4$) and concentrated under reduced pressure to give the product mixture as a gummy material. Pure hydroxyacetophenones were obtained in either case by column chromatography over silica gel G (100-200 mesh) followed by crystallisation from appropriate solvent. All the products were identified by their physical, chemical and spectral data (IR, UV and ^1H NMR) and by comparing with authentic samples.

(i) *Reaction with resorcinol*

Reaction opf resorcinol (10 g, 0.09 mol) with Ac_2O (17 ml, 0.18 mol) and $ZnCl_2$ (24.59 g, 0.18 mol) gave an orange red solid (20 g), which on silica gel (250 g) column chromatography yielded 3-acetyl-2,4-dihydroxyacetophenone (**2**) [column fractions 20-40, hexane-benzene, 8:2, each 1000 ml] as colourless shining plates from benzene (1.2 g), m.p. 90°; dimethyl ether, m.p. 63° (lit.[14a,15], m.p. 95-96°, 65°); 5-acetyl-2,4-dihydroxyacetophenone (**1**) [column fractions, 60-100, hexane-benzene, 1:1, each 1000 ml] as long colourless needles from methanol (15 g), m.p. 178-79°; diacetate, m.p. 120°; dibenzoate, m.p. 118°; dimethyl ether, m.p. 170° (lit.[14a], m.p. 185°, 120°, 118°, 171.5°); and 2,4-dihydroxyacetophenone (**3**) [column fractions, 120-30, benzene, each 1000 ml] as colourless needles from water (300 mg), m.p. 144° (lit.[14a], m.p. 142-44°).

(ii) *Reaction with phenol*

Treatment of phenol (8.8 ml, 0.1 mol) with Ac_2O (11.8 ml, 0.125 mol) and $ZnCl_2$ (17 g, 0.125 mol) gave a dark reddish gummy product (15 g), which on silica gel (225 g) column chromatography yielded 2-hydroxyacetophenone (**4**) [column fractions, 15-30, hexane-benzene, 9:1, each 500 ml) as pale yellow liquid (4.8 g), b.p. 213-14°; acetate, m.p. 87-88°; oxime, m.p. 116-17° (lit.[14b], b.p. 213° and m.p. 89°, 117°); 4-hydroxyacetophenone (**5**) [column fractions, 50-75, benzene, each 500 ml] as shinging needles from ethyl alcohol (5.4 g), m.p. 104-6°; oxime, m.p. 144° (lit.[14b], m.p. 109°, 144-45°).

(iii) *Reaction with hydroquinone*

Treatment of hydroquinone (5.5 g, 0.05 mol) with Ac_2O (9.4 ml, 0.1 mol) and $ZnCl_2$ (13.6 g, 0.1 mol) gave a dark brown product mixture (5.5 g, 0.05 mol), which on silica gel (150 g) column chromatography yielded 2,5-dihydroxyacetophenone (**6**) [column fractions, 20-45, benzene, each 500 ml], as yellowish green leaflets from dil. ethanol (4.2 g), m.p. 200°; oxime, m.p. 149°; diacetate, m.p. 65° (lit.[14c], m.p. 202°, 149-50°, 68°).

(iv) *Reaction with catechol*

Treatment of catechol (5.5 g, 0.05 mol) with Ac_2O (16.6 ml, 0.15 mol) and $ZnCl_2$ (20.4 g, 0.15 mol) gave a dark red gummy material (9 g) which on silica gel (175 g) column chromatography yielded 3-acetoxy-4-hydroxyacetophenone (**7**) [column fractions, 15-25, benzene each 250 ml] as pale brown prisms from n-hexane (450 mg), m.p. 74-76° and 3,4-dihydroxyacetophenone (**8**) [column fractions 45-60, benzene-ethyl acetate, 75:25, each 250 ml] as pale orange red prisms (2.25 g), m.p. 116°; diacetate, m.p. 89°; oxime, m.p. 180° (lit.[14d], m.p. 116°, 91°, 184°).

(v) *Reaction with phloroglucinol*

Reaction of phloroglucinol (6.3 g, 0.05 mol) with Ac_2O (16 ml, 0.15 mol) and $ZnCl_2$ (20.4 g, 0.15 mol) gave an orange red precipitate (10 g), which on silica

gel (200 g) column chromatography yielded 2,4,6-trihydroxyacetophenone (**9**) [column fractions, 15-30, benzene-ethyl acetate, each 250 ml] as orange yellow needles from hot water (3.4 g), m.p. 214-16°; triacetate, m.p. 103°; tribenzoate, m.p. 116° (lit.[14e], m.p. 219°, 103°, 117-18°) and 5-acetyl-2,4,5-trihydroxyacetophenone (**10**) [column fractions, 46-60, benzene-ethyl acetate, 6:4, each 250 ml] as pale violet prisms (2.16 g), m.p. 173°; triacetate, m.p. 93° (lit.[16], m.p. 170°, 92-93°).

(vi) *Reaction with pyrogallol*

Reaction of pyrogallol (6.3 g, 0.05 mol) with Ac_2O (16 ml, 0.15 mol) and $ZnCl_2$ (20.4 g, 0.15 mol) gave a dark red gummy material (10 g), which on silica gel (200 g) column chromatography yielded 2,3,4-trihydroxyacetophenone (11) [column fractions, 10-35, benzene-ethyl acetate, 7:3, each 250 ml] as yellow flakes from dil. ethanol (3.3 g), m.p. 171-73°; triacetate, m.p. 85-86° (lit.[14e], m.p. 173°, 85°).

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Studies on the Pyridylpyrazolone System: Part V† – Cyclocondensation of 1-Phenyl-3-(3′-pyridyl)-2-pyrazolin-5-one with Ethyl Acetoacetate & Related Compounds

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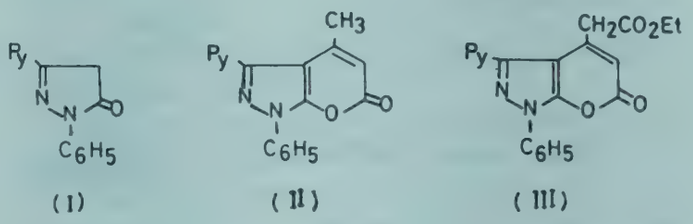
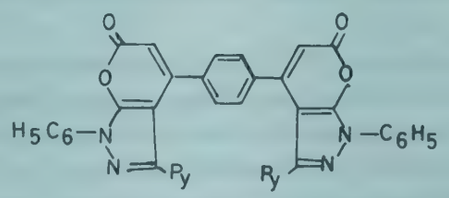
The reaction of 1-phenyl-3-(3′-pyridyl)-2-pyrazolin-5-one (I) with ethyl acetoacetate, diethyl acetonedicarboxylate and diethyl β,β-dioxobenzene-1,4-dipropionate yields the corresponding 1*H*-pyrano[2,3-*c*]pyrazolones (II-IV). Compound II is readily converted into the pyrazolopyridone (V). Formylation of I by Vilsmeier reagent gives the corresponding 4-formyl derivative (VIII) which readily reacts with ethyl acetoacetate to give the pyrazolopyran (IX) or the pyranopyrazolone (XII) depending on the reaction condition. The products have been identified by their IR, PMR, ^{13}CNMR and mass spectral data.

Although the cyclocondensation of ethyl acetoacetate with 1,3-disubstituted-5-aminopyrazoles has been studied by several investigators[2-9], the analogous reaction with 1,3-disubstituted-2-pyrazolin-5-one has not been studied much[10,11]. There still exists a disparity in the structures of the products.

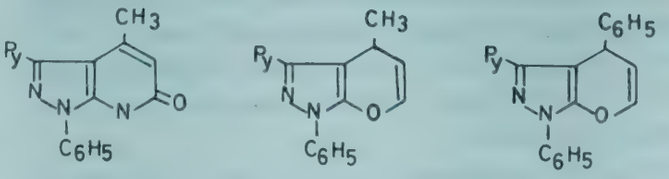
In order to remove this anomaly, the reaction between 1-phenyl-3-(3′-pyridyl)-2-pyrazolin-5-one (I) with ethyl acetoacetate, diethyl acetonedicarboxylate and diethyl *β,β*-dioxobenzene-1,4-dipropionate were investigated at an elevated temperature (150-60°C). The products were identified as 4-methyl-1-phenyl-3-(3′-pyridyl)-1*H*-pyrano[2,3-*c*]pyrazolin-6-one (II), 4-carbethoxymethyl-1-phenyl-3-(3′-pyridyl)-1H-pyrano[2,3-*c*]pyrazolin-6-one (III) and 1,4-bis(1-phenyl-3-(3′-pyridyl)-6(1*H*) oxopyrano[2,3-*c*]pyrazolin-4-yl)benzene (IV), respectively. Compound II failed to undergo condensation with aromatic aldehyde to give the styryl type of products. The IR spectra of II-IV were characterized by a very strong peak at 1775-1780 cm^{-1} which could be attributed to CO of the α-pyrone. The mass spectra of these compounds indicated that the base peak was formed by the elimination of CO_2 from the corresponding molecular ion peak. Thus, compound II gave the base peak at *m/z* 259 (100%) through the loss of CO_2 from the molecular ion peak at *m/z* 303 (28%). The mass spectrum of II was also characterized by a fragment ion at *m/z* 236 (75%) resulting from the elimination of $CH_3.C\equiv CH$ from M^+ through the retro Diels-Alder rearrangement (Chart 1, route-A).



(I) (II) (III)



(IV)



(V) (VI) (VII)

The latter fragment readily lost a molecule of CO_2 to give the fragment ion at *m/z* 219 (22%) which could also be formed from the fragment ion *m/z* 259 by $CH_3.C\equiv CH$ elimination. An alternative fragmentation pattern (Chart 1, route-B) gave a fragment ion at *m/z* 184 (38%) by a process similar to the retro Diels-Alder mechanism followed by loss of phenyl isocyanate from the

†For Part IV of the series see ref. 1.

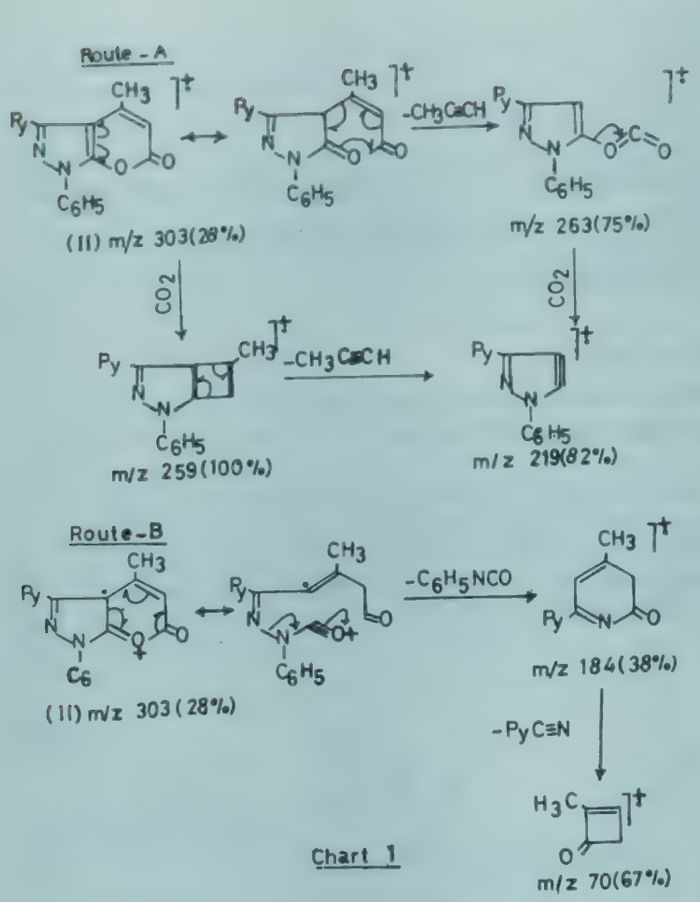
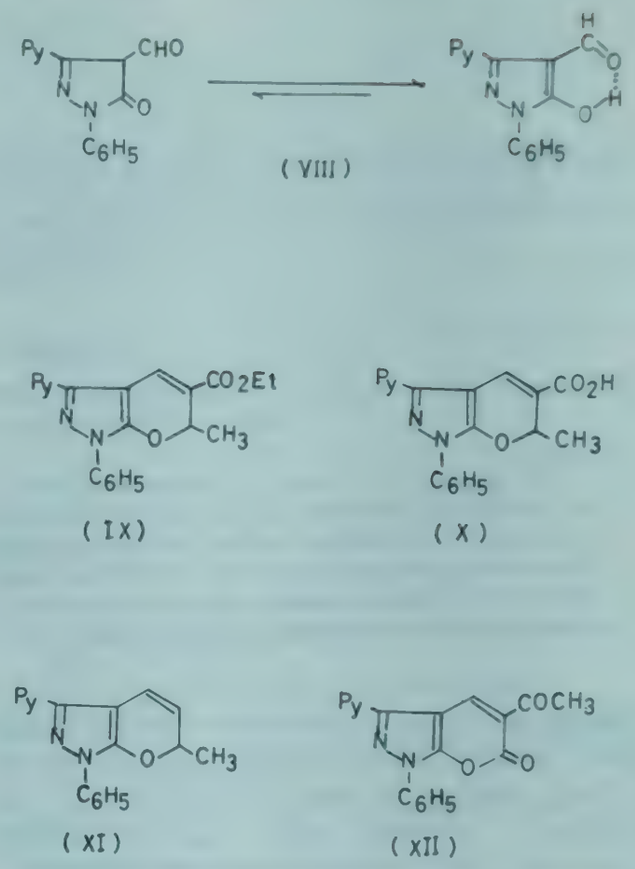


Chart 1



molecular ion. This ion readily lost a molecule of pyridyl cyanide to give the fragment ion at *m/z* 70 (67%).

Conversion of II into the corresponding pyridone V was carried out using either ethanolic ammonia or ammonium carbonate. The structures of both II and V were established on the basis of ^{13}CNMR spectral data by comparing the significant difference between the carbonyl chemical shifts in the isomeric models. The chemical shift of the carbonyl group in both II and V appeared at δ 168.2 and 163.2, respectively. These values are closely matched with those of the two model compounds, 4-methylbenzopyran-2-one (δ CO 167.8 ppm) and 4-methylbenzopyridin-2-one (δ CO 162.8 ppm), thereby supporting the proposed structures.

Another additional proof for the structure II was gathered by converting III into the corresponding carboxylic acid followed by decarboxylation to give a product identical (m.p. IR, PMR and ^{13}CNMR) with II.

On the other hand, cyclocondensation of I with crotonaldehyde or cinnamaldehyde employing a modified procedure as described by Badger *et al.*[12] was carried out to give the correesponding pyranopyrazole VI or VII. The IR spectra of these compounds were characterized by the absence of C=O and the presence of two strong stretching bands due to C=C and C=N functions. Their PMR spectra were also characterized by the *AMX* pattern of the allylic protons (see experimental part). The compound I on treatment with Vilsmeier reagent followed by hydrolysis under basic conditions [13] gave the aldehyde VIII. Its spectral data indicated the predominance of the hydroxy tautomeric form.

The 4-formylpyridylpyrazolone VIII behaved as an *o*-hydroxyaromatic aldehyde. Thus, it reacted readily with ethyl acetoacetate in the presence of a basic catalyst (piperidine under Friedländer condition[14]) to give the corresponding pyranopyrazolone ester derivative IX. The ester IX was hydrolysed with alkali to give the corresponding carboxylic acid X which on decarboxylation furnished 6-methyl-7-phenyl-3-(3′-pyridyl)-1*H*-pyrano[2,3-*c*]pyrazole (XI).

However, cyclocondensation of VIII with ethyl acetoacetate by direct fusion at elevated temperature following the method as described by Fehnel[15] yielded the acetyl pyranopyrazolone derivative XII. The spectral data of XII were in consistence with the proposed structure (see experimental part).

Experimental Procedure

Unless otherwise state, IR spectra were determined in KBr on a Beckmann 4240 spectropho-

tometer (ν_{max} in cm^{-1}), PMR and ^{13}CNMR spectra on a Varian CFT-20 instrument (Chemical shifts in δ, ppm) and mass spectra on a Perkin-Elmer PMU-6E spectrometer using a direct inlet source temperature 90° and beam energy 70 eV.

4-Methyl-1-phenyl-3-(3′-pyridyl)-1H-pyrano[2,3-c]pyrazolin-6-one (II)

A mixture of I (2.4 g; 0.01 mol) and an equimolecular amount of ethyl acetoacetate in gl. acetic acid (50 ml) was heated at reflux temperature for 15 min. The reaction mixture was cooled, filtered and the harvested crystals were washed with ethanol and finally dried *in vacuo* at 100°, yield 1.9 g (63%), m.p. 212°; IR: 1775 (C=O); PMR ($CDCl_3$): 2.87 (3H, *s*, CH_3), 7.35 (1H, *sextet*, Py H-5), 7.46 (1H, *sextet*, Py H-4), 7.8 (1H, *s*, =CH), 7.88 (5H, *m*, N-C_6H_5), 8.52 (1H, *q*, Py H-6), 9.22 (1H, *q*, Py H-2); ($J_{5,4}$=8.03 Hz, $J_{4,6}$=1.76 Hz, $J_{2,6}$=1.13 Hz, $J_{2,5}$=0.88 Hz, $J_{5,6}$=4.87 Hz) (Found: C, 71.0; H, 4.6; N, 13.5. $C_{18}H_{13}N_3O_2$ requires C, 71.3; H, 4.3; N, 13.9%; $M^{+\cdot}$ 303).

4-Carbethoxymethyl-1-phenyl-3-(3′-pyridyl)-1H-pyrano[2,3-c]pyrazolin-6-one (III)

Cyclocondensation of I with diethyl acetonedicarboxylate was carried out as described above to give III, yield 1.8 g (58%), m.p. 223°; IR: 1778 and 1755 (α-pyrone C=O); PMR ($CDCl_3$): 1.5 (3H, *t*, CH_3), 4.3 (2H, *q*, CH_2), 5.1 (2H, *s*, CH_2), 7.4 (1H, *sextet*, Py H-5), 7.52 (1H, *sextet*, Py H-4), 8.82 (1H, *s*, =CH), 7.90 (5H, *m*, N-C_6H_5), 8.60 (1H, *q*, Py H-6), 9.22 (1H, *q*, Py H-2) (Found: C, 67.5; H, 4.6; N, 11.4. $C_{21}H_{17}N_3O_4$ requires C, 67.2; H, 4.5; N, 11.2%; $M^{+\cdot}$ 375).

1,4-Bis[1-phenyl-3-(3′-pyridyl)-6(1H)-oxopyrano[2,3-c]pyrazolin-4-yl]benzene (IV)

Cyclocondensation of I with diethyl β,β-dioxobenzene-1,4-dipropionate was carried out as described above to give IV, yield 2.3 g (65%), m.p. 328°; IR: 1775 (C=O); PMR (DMSO-d_6): 7.19 (4H, *d*, C_6H_4, J=8 Hz), 7.35 (2H, *sextet*, Py H-5), 7.55 (2H, *sextet*, Py H-4), 7.88 (2H, *s*, =CH), 7.90 (10H, *m*, N-C_6H_5), 8.62 (2H, *q*, Py H-6), 9.22 (2H, *q*, Py H-2), (Found: C, 73.5; H, 3.5; N, 13.1. $C_{40}H_{24}N_6O_4$ requires C, 73.6; H, 3.7; N, 12.9%).

4-Methyl-1-phenyl-3-(3′-pyridyl)-1H-pyrazolo[3,4-b]pyridin-6-one (V)

Method (A)

Dry ammonia was passed through a solution of II (3.0 g) in ethanol (50 ml) for 3 hr. The resultant yellow solid was filtered, washed with ethanol several times and recrystallized from ethanol as pale yellow needles, yield 2.3 g (78%), m.p. 278°.

Method (B)

Compound II (3.0 g) was fused with ammonium carbonate (10 g) in an oil-bath. The reaction mixture was heated for 1.5 hr until the evolution of ammonia ceased. It was washed with water and ethanol several times. The pale yellow product was crystallised from ethanol, yield 2.1 g (67%) m.p. 278°; IR: 1680 (C=O), 3310 (NH and/or OH); PMR (DMSO-d_6): 2.75 (3H, *s*, CH_3), 6.7 (1H, *s*, =CH), 7.38 (1H, *sextet*, Py H-5), 7.45 (1H, *sextet*, Py H-4), 7.88 (5H, *m*, N-C_6H_5), 8.53 (1H, *q*, Py H-6), 9.15 (1H, *q*, Py H-2) (Found: C, 71.6; H, 4.5; N, 18.3. $C_{18}H_{14}N_4O$ requires C, 71.5; H, 4.7; N, 18.5%; $M^{+\cdot}$ 302).

4-Methyl/phenyl-1-phenyl-3-(3′-pyridyl)-1H-pyrano[2,3-c]pyrazole (VI/VII)

Employing a modified procedure described by Badger and coworkers[12], a solution of I (4.8 g; 0.02 mol) in gl. acetic acid (100 ml) was cooled while conc. H_2SO_4 (2 ml) added to it with stirring. Thereafter, a solution of anhyd. crotonaldehyde or cinnamaldehyde (0.021 mol) in gl. acetic acid (30 ml) was added to it. The resulting reaction mixture was stirred for 1 hr at room temperature and then heated at reflux temperature for another 1 hr. The coloured solution was concentrated *in vacuo*, the residue dissolved in water (300 ml), rendered basic with NaOH solution (15%) and extracted with chloroform. The combined extracts were dried (anhyd. $MgSO_4$) and solvent removed *in vacuo*. The solid product thus obtained was crystallized from benzene to give VI or VII. Their characterization data are as follows:

VI: yield 2.5 g (53%), m.p. 132°; IR: 1600 (C=C); PMR ($CDCl_3$): 2.80 (3H, *d*, CH_3), 3.80 (1H, *m*, C_4-H), 4.80 (1H, *q*, C_5−H), 6.70 (1H, *d*, C_6−H), 7.35 (1H, *sextet*, Py H-5), 7.52 (1H, *sextet*, Py H-4), 7.92 (5H, *m*, N-C_6H_5), 8.55 (1H, *q*, Py H-6), 9.20 (1H, *q*, Py H-2) (Found: C, 74.6; H, 5.2; N, 14.5. $C_{18}H_{15}N_3O$ requires C, 74.7; H, 5.2; N, 14.5%; $M^{+\cdot}$ 289).

VII: yield 3.1 g (48%), m.p. 158°; IR: 1600 (C=C); PMR ($CDCl_3$): 3.90 (1H, *m*, C_4-H), 5.10 (1H, *q*, C_5−H), 6.95 (1H, *d*, C_6−H), 7.10 (5H, *m*, C_6H_5), 7.30 (1H, *sextet*, Py H-5), 7.65 (1H, *sextet*, Py H-4), 7.90 (5H, *m*, N-C_6H_5), 8.43 (1H, *q*, Py H-6), 9.15 (1H, *q*, Py H-2) (Found: C, 78.8; H, 4.8; N, 11.9. $C_{23}H_{17}N_3O$ requires C, 78.8; H, 4.9; N, 12.0%; $M^{+\cdot}$ 351).

4-Formyl-1-phenyl-3-(3'-pyridyl)-2-pyrazolin-5-one (VIII)

A solution of I (11.8 g; 0.5 mol) in DMF (146 g; 2.0 mol) was treated with $POCl_3$ (32.1 g; 2.1 mol) in a dropwise fashion during 2 hr with stirring. The reaction mixture was stirred at 80-90° for 2.5 hr and allowed to remain at room temperature overnight. It was poured onto ice and neutralised with NaOH solution (50%). The coloured oily layer, thus separated, was extracted repeatedly with chloroform. The combined extract was washed with water, dried (anhyd. $MgSO_4$) and filtered. The creamy coloured solid, obtained by removal of solvent *in vacuo* was crystallised from pet. ether (50-70°) to give VIII, yield 5.6 g (43%), m.p. 88-90°; IR: 1710 (C=O) and 1700 (C=O); PMR ($CDCl_3$): 6.20 (1H, *d*, C_4-H), 4.80 (1H, *bs*, OH), 7.30 (1H, *sextet*, Py H-5), 7.55 (1H, *sextet*, Py H-4), 7.93 (5H, *m*, N-C_6H_5), 8.62 (1H, *q*, Py H-6) 9.20 (1H, *q*, Py H-2), 9.95 (1H, *s*, OH), (Found: C, 67.8; H, 4.2; N, 15.6. $C_{15}H_{11}N_3O_2$ requires C, 67.9; H, 4.2; N, 15.8%; $M^{+\cdot}$ 265).

5-Carbethoxy-6-methyl-1-phenyl-3-(3'-pyridyl)-1H-pyrano[2,3-c]pyrazole IX

A stirred mixture of VIII (6.6g: 0.025 mol), ethyl acetoacetate (6.8 g; 0.05 mol) and piperidine (150 ml) was heated at reflux temperature for 3 hr, filtered while hot, cooled and concentrated when a pale yellow substance separated out. It was crystallized from benzene to afford IX as colourless needles, yield 4.2 g (53%), m.p. 123-24°; IR: 1775 (C=O): PMR (DMSO-d_6): 1.50 (3H, *t*, CH_3), 1.90 (3H, *d*, $C-CH_3$), 4.20 (2H, *q*, CH_2) 4.80 (1H, *q*, OCH), 7.95 (5H, *m*, N-C_6H_5), 7.45 (1H, *sextet*, Py H-5), 7.63 (1H, *sextet*, Py H-4), 8.55 (1H, *s*, =CH), 8.65 (1H, *q*, Py H-6), 9.15 (1H, *q*, Py H-2) (Found: C, 69.6; H, 5.2; N, 11.7. $C_{21}H_{19}N_3O_3$ requires C, 69.8; H, 5.3; N, 11.6%; $M^{+\cdot}$ 361).

6-Methyl-1-phenyl-3-(3'-pyridyl)-1H-pyrano[3,4-b]pyrazole-5-carboxylic acid (X)

A mixture of IX (3.6 g; 0.01 mol), 6 *N* KOH solution (100 ml) and ethanol (300 ml) was stirred at reflux temperature for 3 hr, cooled and acidified with HCl (6*N*). The crude acid was filtered, washed with water, crystallised from ethanol-water (2:1, v/v) and dried *in vacuo* at 90°, yield 3.1 g (92%), m.p. 302°; IR: 1690 (C=O), 3500 (OH); PMR (CF_3COOH): 2.05 (3H, *d*, CH_3), 4.35 (1H, *q*, OCH), 7.90 (5H, *m*, N-C_6H_5), 7.45 (1H, *sextet*, Py H-5), 7.62 (1H, *sextet*, Py H-4), 8.55 (1H, *s*, =CH), 8.65 (1H, *q*, Py H-6), 9.15 (1H, *q*, Py H-2), 11.50 (1H, *bs*, OH), (Found: C, 68.2; H, 4.4; N, 12.5. $C_{19}H_{15}N_3O_3$ requires C, 68.5; H, 4.5; N, 12.6%; $M^{+\cdot}$ 333).

6-Methyl-1-phenyl-3-(3'pyridyl)-1H-pyrano[2,3-c]pyrazole (XI)

The finely pulverized potassium salt of X (5.5 g; 0.015 mol) was thoroughly mixed with calcium oxide (10.5 g) and the mixture heated under reflux over a full flame of Meker burner. The decarboxylation product was collected as a yellow coloured distillate, yield 3.6 g (60%). It was dissolved in ether, dried (anhyd. $MgSO_4$), filtered and solvent evaporated *in vacuo* to afford XI as a pale yellow crude product which recrystallised from benzene, m.p. 112-13°; IR: 1620 (C=C); PMR ($CDCl_3$): 1.90 (3H, *d*, CH_3), 4.35 (1H, *m*, O−CH), 5.62 and 6.68 (2H, *q*, CH=CH); 7.45 (1H, *sextet*, Py H-5), 7.55 (1H, *sextet*, Py H-4), 7.90 (5H, *m*, N-C_6H_5), 8.65 (1H, *q*, Py H-6), 9.10 (1H, *q*, Py H-2), (Found: C, 74.5; H, 5.1; N, 14.3. $C_{18}H_{15}N_3O$ requires C, 74.7; H, 5.2; N, 14.5%; $M^{+\cdot}$ 289).

5-Acetyl-1-phenyl-3-(3'-pyridyl)-1H-pyrano[2,3-c]pyrazolin-5-one (XII)

A mixture of VIII (2.7 g; 0.01 mol) and ethyl acetoacetate (50 ml) was heated for 1 hr in an oil-bath maintained at 160-170°. The white solid obtained on cooling, was collected, washed with ethanol, crystallised from ethanol and dried at 90° *in vacuo* to give XII, yield 1.3 g, (65%), m.p. 169-68°; IR: 1775 (C=O), 1715 (C=O); PMR (DMSO-d_6): 2.40 (3H, s, $COCH_3$); 7.40 (1H, *sextet*, Py H-5), 7.58 (1H, *sextet*, Py H-4), 7.95 (5H, *m*, N-C_6H_5); 8.45 (1H, *s*, =CH), 8.58 (1H, *q*, Py H-6), 9.22 (1H, *q*, Py H-2) (Found: C, 68.7; H, 3.9; N, 12.6. $C_{19}H_{13}N_3O_3$ requires C, 68.9; H, 4.0; N, 12.7%; $M^{+\cdot}$ 331).

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Synthesis of Azoles & Fused Azoles from α-Arylhydrazononitriles

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The reaction of α-arylhydrazononitriles (I) with phenylhydrazine, hydrazine hydrate, *o*-phenylenediamine, mercaptoacetic acid and phenyl isothiocyanate gives amidrazone (IIa-c, III), pyrazolone (IVa-c), benzimidazole (X), 4-thiazolone (XIe,d) and 1,2,4-triazinthione (XII) derivatives respectively. Compound IIa reacts with ethyl chloroformate to give amidrazone V which on base-catalyzed cyclization affords the triazolone VI. However, it reacts with nitrous acid to give the tetrazole VII. The condensation of IVa with ethyl α-chloroacetoacetate and IVe with α-cyanocinnamonitrile furnishes the pyrazolo[1,5-*a*]imidazole (VIII) and pyrano[3,2-*b*]pyrazole (IX) derivatives respectively.

The importance of arylhydrazono-α-cyano derivatives as antitubercular agents and oxidative phosphorylation inhibitors[1-4], has recently stimulated the interest in the synthesis and chemistry of such compounds. In continuation of our work[5-8] on the synthesis of heterocyclic compounds, we now report the utility of α-arylhydraqzononitriles (I) in the synhthesis of azoles and fused azoles.

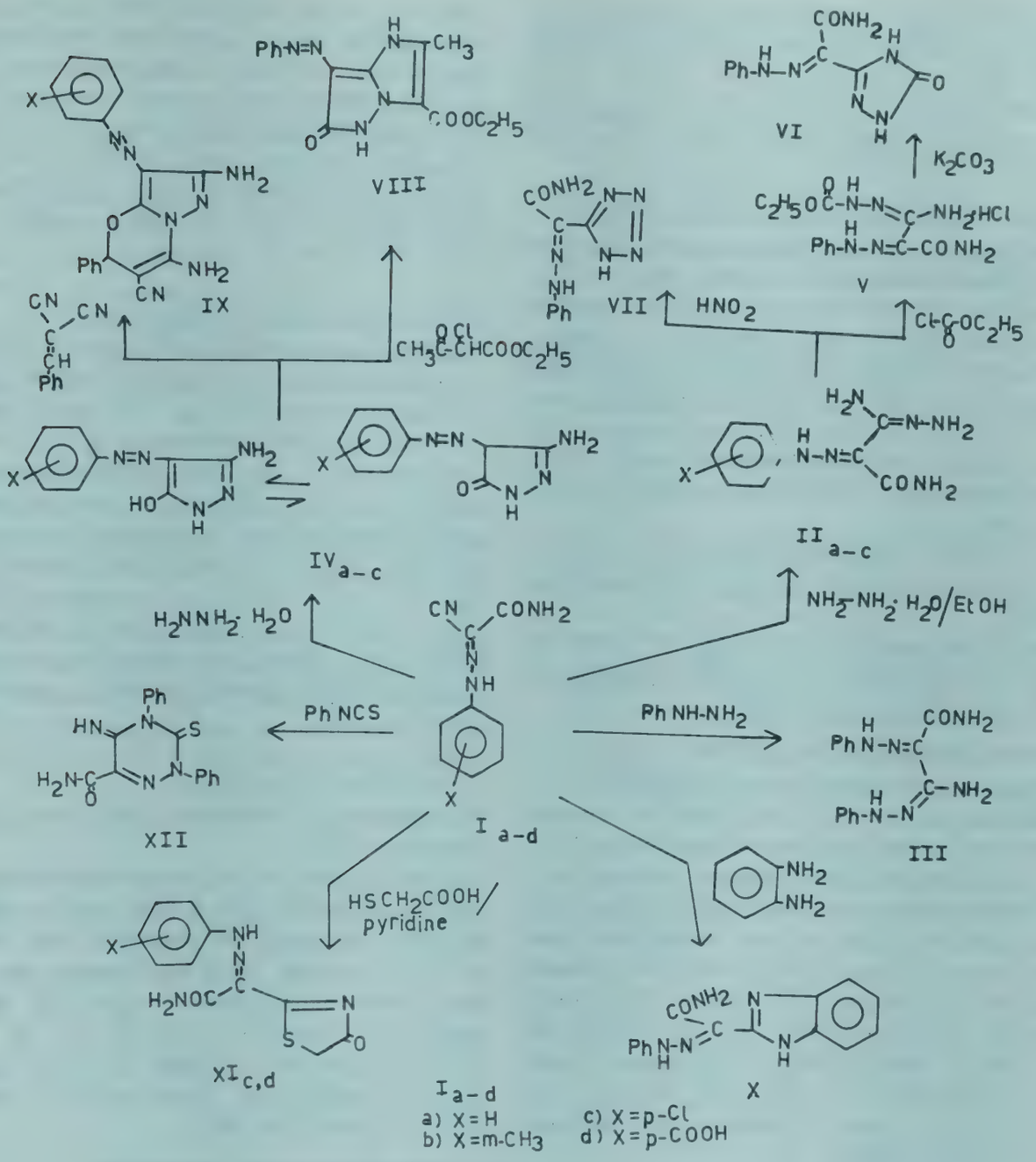
The reaction of I with hydrazine hydrate in ethanol yielded the corresponding amidrazone derivatives (IIa-c); however, in the absence of a solvent the pyrazolones (IVa-c) were the products. The reaction of α-carboxamido-α-phenylhydrazonoacetonitrile (Ia) with phenylhydrazine, *o*-phenylenediamine and phenyl isothiocyanate furnished the phenylamidrazone (III), benzimidazole (X) and 1,2,4-triazinthione (XII) derivative respectively (Scheme 1). A similar condensation of Ie,d with mercaptoacetic acid resulted in the formation of 4-thiazolone derivatives (XIe,d). The compound IIa when reacted with ethyl chloroformate gave V which on base-catalyzed cyclization afforded the triazolone (VI) while with nitrous acid it yielded another heterocyclic system, the tetrazole (VII). The reaction of IVa with ethyl α-chloroacetoacetate and of IVc with α-cyanocinnamonitrile yielded the pyrazolo[1,5-*a*]imidazole (VIII) and pyrano[3,2-*b*]pyrazole (IX) derivatives respectively (Scheme 1). The structures II, V, VI, VIII-X and XII were established by elemental analyses and IR and PMR spectral data. The PMR spectra of IIa-c showed signals for seven protons of NH and NH_2 at δ 6.0, 6.6, 7.2 and 11.5 and aromatic protons at 7.3-7.8. The appearance of ethyl proton signals at δ 1.2 (*t*, CH_3) and 4.15 (*q*, CH_2) and the absence of these signals in the spectra of V and VI were tenable with the proposed structures. The formation of IX was presumed to proceed via initial addition of the hydroxyl group in IV to the activated double bond of Ia followed by cyclization of the ring nitrogen and cyano group to IX[9]. The formation of X involved the initial addition of an amino group of *o*-phenylenediamine to the cyano group of Ia followed by cyclization with the loss of ammonia. Compound XI was presumed to have resulted from the addition of mercaptoacetic acid to the C≡N instead of C=N followed by cyclization[10-12]. The formation of XII involved addition of NH of Ia to the C=N function of phenyl isothiocyanate and subsequent cyclization.

Experimental Procedure

All melting points are uncorrected. IR spectra were recorded in KBr on a Pye-Unicam SP-1100 spectrometer (ν_{max} in cm^{-1}), and PMR spectra in $CDCl_3$ on a Varian 60 MHz spectrometer using TMS as internal reference (chemical shift in δ, ppm). Elemental analyses were carried out at the Cairo Analytical Center at Cairo University.

α-*Carboxamido*-α-*phenylhydrazonoacetonitrile* (*Ia*)

To a solution of cyanoacetamide (0.1 mol) and anhyd. sodium acetate (3.5 g) in ethanol (100 ml) and water (10 ml) was added a solution of benzenediazonium chloride (0.1 mol) in water (50 ml) under continuous stirring in an ice-bath (0-5°) for 30 min. The reaction mixture was further stirred for 2 hr at room temperature and the resulting product filtered off, washed with water and crystallized from acetic acid to give Ia, m.p. 230°, yield 80% (Found: C, 57.2; H, 4.1; N, 29.5. $C_9H_8N_4O$ requires C, 57.4; H, 4.2; N, 29.8%); IR: 1605 (C=N), 1660 (C=O), 2220 (C≡N) and 3140-3300 (NH); PMR: 6.7, 6.9 (each *s*, 3H, NH



Scheme 1

and NH_2), 7.1-7.6 (*m*, 5H, Ar-*H*). Other members of the series prepared similarly were:

Ib: m.p. 220°, yield 75% (Found: C, 59.3; H, 4.7; N, 27.6. $C_{10}H_{10}N_4O$ requires C, 59.4; H, 4.9; N, 27.7%).

Ic: m.p. 260°, yield 88% (Found: C, 48.4; H, 3.1; N, 24.9; Cl, 15.7. $C_9H_7N_4OCl$ requires C, 48.5; H, 3.1; N, 25.1; Cl, 15.7%).

Id: m.p. 270°, yield 82% (Found: C, 51.4; H, 3.1; N, 23.9. $C_{10}H_8N_4O$ requires C, 51.7; H, 3.4; N, 24.1%).

α-Carboxamido-α-phenylhydrazonoacetamidrazone (IIa)

A mixture of Ia (1.88 g, 0.1 mol) and hydrazine hydrate (0.7 g, 0.12 mol) in ethanol (50 ml) was refluxed for 1 hr and the reaction mixture poured into ice-water. The solid thus separated was collected and crystallized from ethanol to give IIa, m.p. 125°, yield 65% (Found: C, 48.8; H, 5.2; N, 37.8. $C_9H_{12}N_6O$ requires C, 49.1; H, 5.4; N, 38.1%); IR: 1610 (C=N), 1665 (C=O), 3000-3350 (NH, NH_2); PMR: 6.0, 6.6, 7.2 and 11.5 (each *s*, 7H, NH and NH_2), 7.3-7.8 (*m*, 5H, Ar−*H*). Other compounds prepared similarly were:

IIb: m.p. 135°, yield 68% (Found: C, 51.1; H, 5.8; N, 35.6. $C_{10}H_{14}N_6O$ requires C, 51.2; H, 6.0; N, 35.9%).

IIc: m.p. 162°, yield 73% (Found: C, 41.1; H, 4.1; N, 32.7; Cl, 13.9. $C_9H_{11}N_6OCl$ requires C, 41.2; H, 4.3; N, 33.0; Cl, 13.9%).

III: m.p. 195°, yield 75% (FOund: C, 60.6; H, 5.2; N, 28.0. $C_{15}H_{16}N_6O$ requires C, 60.8; H, 5.4; N, 28.3%); IR: 1600 (C=N), 1670 (C=O), 3100-3350 (NH); PMR: 6.7, 6.8, 6.9, 8.5, 13.8 and 14.5 (each *s*, 6H, NH and NH_2), 7.0-7.7 (*m*, 10H, Ar − *H*).

3-Amino-5-hydroxy-4-phenylazopyrazole (IVa)

A mixture of Ia and hydrazine hydrate was fused without solvent on a water-bath for 2 hr. The reaction mixture was cooled and washed with ethanol. The resulting solid was crystallized from ethanol to give IVa, m.p. 238°, yield 96% (Found: C, 52.9; H, 4.2; N, 34.1. $C_9H_5N_5O$ requires C, 53.2; H, 4.4; N, 34.4%); IR: 1620 (C=N), 1650 (C=O), 3150-3450 (NH); PMR: 6.2, 6.9, 10.9 (each *s*, 4H, NH and NH_2), 7.2-7.8 (*m*, 5H, Ar − *H*).

IVb: m.p. 236°, yield 94% (Found: C, 55.1; H, 4.9; N, 32.1. $C_{10}H_{11}N_5O$ requires C, 55.3; H, 5.0; N, 32.2%).

IVc: m.p. 270°, yield 95% (Found: C, 75..3; H, 5.2; N, 29.1; Cl, 19.8. $C_{15}H_{13}N_5OCl$ requires C, 75.5; H, 5.4; N, 29.4; Cl, 14.9%).

α(N-Ethoxycarbonylamidrazonyl)-α-phenylhydrazonoacetamide hydrochloride (V)

A solution of IIa (2.2 g, 0.01 mol) in ethanol (100 ml) was treated with ethyl chloroformate (1.1 g, 0.01 mol) and the reaction mixture refluxed for 3 hr and evaporated to one third of its volume. The solid product thus obtained was crystallized from ethanol to give V, m.p. 209°, yield 68% (Found: C, 43.5; H, 5.3; N, 25.2; Cl, 10.6. $C_{12}H_{18}N_6O_3Cl$ requires C, 43.7; H, 5.4; N, 25.5; Cl, 10.7%); IR: 1605 (C=N), 1665 (C=O), 1720 (ester), 3000-3300 (NH); PMR: 1.2 (*t*, 3H, CH_3), 4.15 (*q*, 2H, CH_2), 6, 6.9, 8.2 and 15 (each *s*, 6H, NH and NH_2), 7.1-7.5 (*m*, 5H, Ar − *H*).

5-[Phenylhydrazono-(carbamoyl)-methyl]-1,2,4-triazol-3-one (VI)

A suspension of V in aq. K_2CO_3 was refluxed for 2 hr, and the reaction mixture cooled and neutralized with HCl. The solid product thus separated was crystallized from ethanol to give VI, m.p. 180°, yield 75% (Found: C, 51.9; H, 4.1; N, 36.2. $C_{10}H_{10}N_6O$ requires C, 52.1; H, 4.3 N, 36.5%); IR: 1600 (C=N), 1660, 1680 (2C=O), 3100-3250 (NH); PMR: 5.1, 6.0, 6.9 and 11.4 (each *s*, 5H, NH and NH_2), 7.2-7.8 (*m*, 5H, Ar − *H*).

5-[Phenylhydrazono-(carbamoyl)-methyl]tetrazole (VII)

To a solution of IIa (2.2 g, 0.01 mol) in acetic acid (50 ml) was added a solution of sodium nitrite (0.7 g, 0.01 mol) in water (2 ml) dropwise with stirring at 0-5°, and the reaction mixture poured into ice-water. The solid thus obtained was crystallized from ethanol to give VII, m.p. 195°, yield 70% (Found: C, 46.4; H, 3.7; N, 42.1. $C_9H_9N_7O$ requires C, 46.7; H, 3.9; N, 42.4%); IR: 1610 (C=N), 1680 (C=O), 3100-3300 (NH); PMR: 6.0, 6.9, 9.7, 14.2 (each *s*, 4H, NH and NH_2), 7.2-7.7 (*m*, 5H, Ar − *H*).

6-Ethoxycarbonyl-5-methyl-2-oxo-3-phenylazopyrazolo[1,5-a]imidazole (VIII)

A mixture of IVa (2 g, 0.01 mol) and ethyl α-chloroacetoacetate (1.5 g, 0.01 mol) in ethanol (50 ml) and triethylamine (2 g, 0.02 mol) was refluxed for 3 hr. The reaction mixture was cooled to room temperature, poured into water and the resultant solid crystallized from ethanol to give VIII, m.p. 246°, yield 58% (Found: C, 57.3; H, 4.7; N, 22.1. $C_{15}H_{15}N_5O_3$ requires C, 57.5; H, 4.8; N, 22.3%); IR: 1605 (C=N), 1650 (C=O), 1710 (ester), 2900-3200 (NH); being insoluble in common NMR solvents, its PMR spectrum could not be recorded.

2,7-diamino-6-cyano-3-(p-chlorophenylazo)-5-hydro-5-phenylpyrazolo[3,2-b]oxazine (IX)

A suspension of α-cyanocinnamonitrile (1.5 g, 0.01 mol) and IVc (2.4 g, 0.01 mol) in ethanol (50 ml) and two drops of piperidine was refluxed 5 hr. The resultant solid was filtered and crystallized from ethanol-DMF to give IX, m.p. 260°, yield 65% (Found: C, 58.1; H, 3.3; N, 25.1; Cl, 8.8. $C_{19}H_{14}N_7OCl$ requires C, 58.2; H, 3.5; N, 25.0; Cl, 9.0%); IR: 1590, 1610 (C=N), 2220 (C≡N), 2930-3200 (NH).

2-[Phenylhydrazono-(carbamoyl)-methyl]benzimidazole (X)

A suspension of Ia (1.9 g, 0.01 mol) and *o*-phenylenediamine (1.1 g, 0.01 mol) in acetic acid (50 ml) was refluxed 6 hr. The reaction mixture was evaporated to half of its volume, poured into ice-water, and the resultant solid crystallized from acetic acid to give X, m.p. 246°, yield 57% (Found: C, 64.3; H, 4.5; N, 24.7. $C_{15}H_{13}N_5O$ requires C, 64.5; H, 4.6; N, 25.0%); IR: 1605 (C=N), 1660 (C=O), 3100-3350 (NH); PMR: 6.1, 6.8, 11.8 (each *s*, 4H, NH and NH_2), 7.2-8.1 (*m*, 9H, Ar − *H*).

2-[p-Chlorophenylhydrazono-(carbamoyl)-methyl]thiazolin-4-one (XIc)

A mixture of Ic (2 g, 0.01 mol) and mercaptoacetic acid (0.9 g, 0.01 mol) in pyridine (30 ml)

was refluxed for 5 hr and the reaction mixture concentrated to half its volume. The solid so separated was crystallized to give XIc, m.p. > 260°, yield 52% (Found: C, 44.3; H, 3.1; N, 18.7; Cl, 11.7; S, 10.7. $C_{11}H_9N_4O_2SCl$ requires C, 44.5; H, 3.0; N, 18.8; Cl, 12.0; S, 10.8%); IR: 1610 (C=N), 1660, 1690 (2CO), 2850-3300 (NH); being insoluble in common NMR solvents, its PMR spectrum could not be recorded.

In a similar way compound XId was prepared from Id and mercaptoacetic acid, m.p. > 260°, yield 55% (Found: C, 46.7; H, 3.1; N, 18.0; S, 10.2. $C_{12}H_{10}N_4O_4S$ requires C, 47.0; H, 3.2; N, 18.3; S, 10.4%).

6-*Carboxamido*-5-*imino*-2,4-*diphenyl*-2,3,4,5-*tetrahydro*-1,2,4-*triazine*-3-*thione* (*XII*)

A solution of compound Ia (1.9 g, 0.01 mol) and phenyl isothiocyanate (1.3 g, 0.01 mol) was refluxed for 5 hr and evaporated *in vacuo*. The solid so obtained was triturated with ethanol and crystallized from pyridine to give XII, m.p. > 260°, yield 62% (Found: C, 59.2; H, 4.1; N, 21.3; S, 9.9. $C_{16}H_{13}N_5OS$ requires C, 59.4; H, 4.0; N, 21.6 S, 9.9%); IR: 1680 (C=O), 3150-3300 (NH); PMR: 5.1, 6.8 (each *s*, 3H, NH and NH_2), 7.3-7.8 (*m*, 10H, Ar−*H*).

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Reaction of 2,6-Diaryl-3-halopyran-4(*H*)-ones with Sodium Hydroxide

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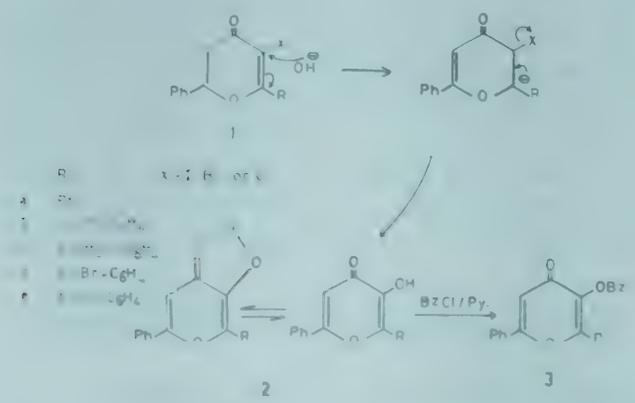
The reaction of 2,6-diaryl-3-halopyran-4(*H*)-ones (**1**) with hydroxide ion in aqueous ethanol leads to 2-aryl-3-hydroxy-4(*H*)-pyrones (**2**) while in absolute ethanol **1a-e** with OH^- afford 3(2*H*)-furanones (**4**) and **2**. Spectral and chemical evidences have been used to assign structures to the above compounds. Pathways for these transformations are suggested.

Several naturally occurring compounds containing hydroxypyran-4(*H*)-one ring system[1] possess pharmaceutical[2], biological[3] and cosmetic[4] properties. Several syntheses of hydroxy-4-pyrones are known, such as the conversion of carbohydrates[5], furan[6] and pyran[7] derivatives as well as cyclization of appropriately substituted ketones[8]. 3-Halo-4(*H*)-pyrones[9] can lead to a series of other functionalized compounds including 3-hydroxy derivatives. 2-Aryl-3-halo-6-phenylpyran-4(*H*)-ones (**1**) possess three centers, viz. positions 2,3 and 6 for nucleophilic attack. Of these positions 2 and 6 are almost equivalent. While attack at C-3 may result in substitution of the halogen[10], an attack at C-2 or C-6 leads to ring-opening[11,12]. The present work is concerned mainly with the reactions of 2,6-diaryl-3-halopyran-4(*H*)-ones (**1**) with hydroxide ion, where it has been possible to control the direction of attack to the position-3 or 2 and 6.

Treatment of **1a-e** with excess sodium hydroxide in aq. ethanol led to, after acidification, 2-aryl-3-hydroxy-6-phenylpyran-4(*H*)-ones (**2a-e**) via substitution reaction[10] at C-3 (Scheme 1). Furthermore, **2d** gave with benzoyl chloride the 3-benzoyloxy derivative (**3d**). It is worthy to mention



Scheme 1

that substitution of a halogen by hydroxide ion, in similar systems has been reported for 6-bromocomenic acid[13] and 2-bromo-3,5-dimethylthiopyran-4(*H*)-one[11].

Treatment of **1a-e** with sodium hydroxide in absolute ethanol led to 3(2*H*)-furanones (**4**) which were characterized by elemental analyses, and IR and PMR data.

The IR spectra of **2** exhibited two absorption bands in the regions 1591-1625 and 3400-3420 cm^{-1} for the chelated carbonyl and hydroxy groups, respectively, characteristic of 3-hydroxypyrones[14]. Their PMR spectra exhibited a singlet in the region δ 6.34-7.07 for the H-5 ring proton (Table 1) almost in the same region reported for other 3-hydroxypyrones[14,15].

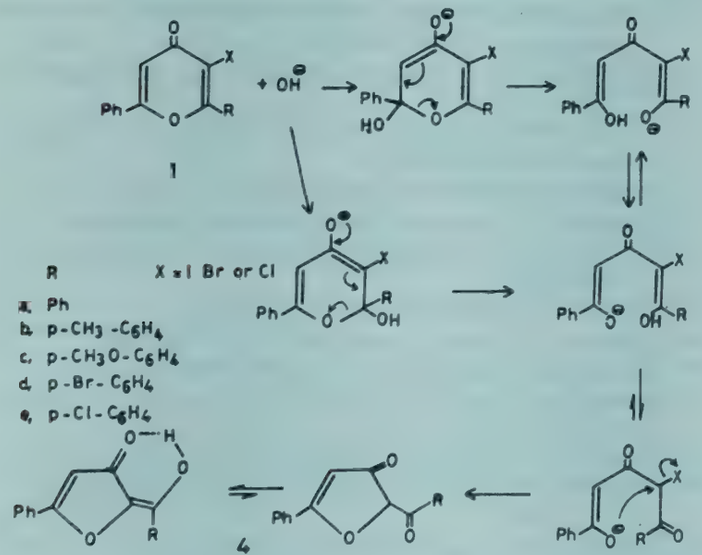
Moreover, the mass spectra of the 3-hydroxy-4-pyrones (**2a,e**) gave moderately intense molecular ion peaks. The major fragmentation route involved expulsion of oxygen atom from the molecular ion peak followed by hydrogen migration giving an intense peak due to pyran-4(*H*)-one. The latter gave rise to a series of peaks characteristic of pyran-4(*H*)-ones[16].

2,6-Diarylpyran-4(*H*)-ones undergo ring-opening on treatment with hydroxide ion giving 1,5-diarylpent-1,3,5-triones[17]. On the other hand, 2-bromo-3,5-dimethylthiopyran-4(*H*)-one and thiopyran-4(*H*)-thiones are also ring-opened with hydroxide ion with subsequent cyclization into a pyran-1,3-dithione[11] and 3(*H*)-acylmethylene-1,2-dithiole derivatives[18], respectively. However, in the present study, the reaction of the 3-halopyrones (**1a-e**) with ethanolic sodium hydroxide gave two types of products, viz. 3(2*H*)-furanone derivatives (**4a-e**) and 3-hydroxy-4(*H*)-pyrones (**2a-e**).

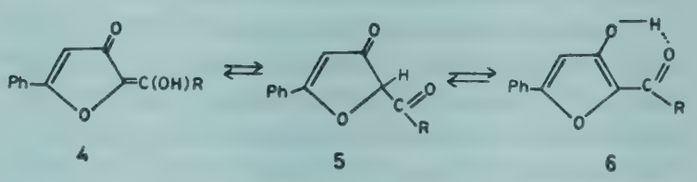
The formation of **4** from **1** may be rationalized as shown in Scheme 2. The OH^- attacks preferentially C_2- or C_6-leading to ring-opening, elimi-

Table 1—Characterization Data of 3-Hydroxy-4-pyrones (**2**) and 3(2*H*)-Furanones (**4**)

Compd	m.p. °C	Mol. formula	Found (%) (Calc.) C	H	X	PMR (δ, DMSO-d_6) H-4 (*s*)	H-5 (*s*)	Ar–H (*m*)	Others (*s*)
2a	245	$C_{17}H_{12}O_3$	77.2 (77.3	4.7 4.6	— —)		6.77	7.67	
2b	240	$C_{18}H_{14}O_3$	77.7 (77.7	5.3 5.1	— —)		6.37	7.55	2.34 (CH_3)
2c	242	$C_{18}H_{14}O_4$	73.8 (73.5	5.2 5.0	— —)		6.34	7.30	3.80 (OCH_3)
2d	235	$C_{17}H_{11}BrO_3$	59.2 (59.5	3.0 3.2	22.9 23.3)		6.57	7.77	
2e	232	$C_{17}H_{11}ClO_3$	68.3 (68.4	3.9 3.7	11.5 11.9)		7.07	7.75	
3d	210	$C_{24}H_{15}BrO_4$	64.2 (64.4	3.5 3.4	17.7 17.9)		6.72	7.68	
4a	250	$C_{17}H_{12}O_3$	77.5 (77.3	4.4 4.6	— —)	6.50		7.60	
4b	255	$C_{18}H_{14}O_3$	77.5 (77.7	5.0 5.1	— —)	6.46		7.40	2.50 (OCH_3)
4c	261	$C_{18}H_{14}O_4$	73.3 (73.5	5.2 5.0	— —)	6.42		7.25	3.83 (OCH_3)
4d	272	$C_{17}H_{11}BrO_3$	59.3 (59.5	3.4 3.2	23.0 23.3)	6.50		7.89	
4e	260	$C_{17}H_{11}ClO_3$	68.6 (68.4	3.9 3.7	11.5 11.9)	6.40		7.87	



Scheme 2



nation of halide ion and subsequent recyclization. On the other hand, formation of **2** under the same conditions is the result of the direct attack of OH^- at position-3 of the ring.

Three tautomeric structures **4**, **5** and **6** can be considered for the furanones. However, the spectral data of these compounds indicate that tautomer **4** is the most predominant one. Their IR spectra exhibited a broad carbonyl absorption in the range of 1575-1610 cm^{-1} as well as νOH in the region 3300-3350 cm^{-1}. Their PMR spectra displayed a singlet at δ 6.40-6.50 for the C_4-ring proton, similar to that reported for several 4-unsubstituted furan-3(2*H*)-ones[19]. The disappearance of the C_2-ring proton in the spectra excludes the tautomer **5**. Moreover, 2-benzoyl-5-phenylfuran-3(2*H*)-one (**6a**) synthesised earlier[19] by another route was found to be completely different (m.p., IR and PMR) from our product **4a**.

E and *Z* isomerism is possible in the case of arylmethylenefuranones. The *E*-configuration is tentatively assigned to the furanones (**4**) since it is expected to be more favoured due to intramolecular hydrogen bonding[19,20].

Experimental Procedure

IR spectra were recorded in KBr on a Unicam SP 1025 spectrophotometer (ν_{max} in cm^{-1}), UV spectrum on a Unicam SP 800 spectrophotometer, PMR spectra on a Varian EM-390 90 MHz spectrometer using TMS as internal standard and mass spectra on an AEI MS 30 spectrometer. TLC was performed on Merck kieselgel 60-F 254 precoated plastic plates.

3-Iodo-, 3-bromo- and 3-chloro-2-aryl-6-phenylpyran-4(*H*)-ones (**1**) were prepared by the reaction of 1,5-diarylpent-1-yne-3,5-diones with iodine monochloride[9a], NBS[9b] and N-chlorosuccinimide[9c], respectively, as described earlier.

2-Aryl-3-hydroxy-6-phenyl-pyran-4(H)-ones (**2**; Table 1)

A solution of **1a-e** (X=I, Br or Cl) (0.5 g; 0.0013 mol) in ethanol (10 ml) was refluxed with sodium hydroxide (0.3 g; 0.0075 mol) in water (2 ml) for 1-2 hr. The yellow solution was concentrated, diluted with cold water and acidified with 10% sulfuric acid. The separated **2a-e** were filtered, washed with water and crystallized from ethanol in yellow needles, yield 71-85%. **2a:** λ_{max} (saturated solution in methanol) 254, 284, 374 nm; MS: *m/z* 264 (M^+, 4), 263 (12), 248 (4), 220 (12), 115 (8), 105 (100), 102 (17), 77 (60); **2e**: *m/z* 300 (M^+), 298 (4,8), 299, 297 (3,5), 284, 282 (22, 50), 256, 254 (35, 100), 151, 149 (2,5), 141, 139 (6, 12), 138, 136 (5, 10), 115 (55), 113 (4), 111 (10), 105 (19), 102 (21), 77 (16).

2-(p-Bromophenyl)-3-benzoyloxy-6-phenyl-pyran-4(H)-one (**3d**; Table 1)

A mixture containing a solution of **2d** (0.4 g; 0.0012 mol) in dry pyridine (5 ml) and benzoyl chloride (1 ml, 0.0086 mol) was kept stirred overnight, diluted with cold water and the separated 3-benzoyloxy-pyrone (**3d**) was filtered, washed with water and crystallized from methanol in needles, yield 0.4 g (77%).

2-(Aryl-hydroxymethylene)-5-phenyl-3(2H)-furanones (**4a-e**; Table 1)

A solution of **1a-e** (X=I, Br or Cl) (0.5 g; 0.0013 mol) in abs. ethanol (10 ml) was added to a solution of sodium hydroxide (0.5 g; 0.0125 mol) in abs. ethanol (5 ml). After refluxing for 2 hr yellow precipitate which separated was filtered, washed with ethanol, dissolved in cold water (15 ml) and then acidified with 5 *M* sulfuric acid (3 ml). The separated furanones (**4a-e**) (yield 55-65%) were crystallized from methanol in yellow needles.

The ethanol mother liquor was evaporated under reduced pressure and the residue was treated with cold water (10 ml), acidified with 10% sulfuric acid and the precipitated 3-hydroxypyrones (**2a-e**) (yield 20-35%) were filtered, washed with water, dried and crystallized from ethanol.

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Facile Formation of 9,11-Secoestrane-11,17-oxides from Corresponding 9,11-Secoestranes†

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9,11-Secoestradiol derivatives having a hydroxyl group at C-11 or a 11-oic acid undergo facile cyclisation at C-17 giving corresponding 11, 17-oxides. Formation of 3-methoxy-11-oxo-9, 11-secoestrane-11, 17-oxide (**2**), 3-methoxy-9, 11-secoestrane-11,17-oxide (**3**), 3-methoxy-11-methyl-9, 11-secoestrane-11,17-oxide (**5**) and 3-methoxy-11,11-dimethyl-9,11-secoestrane-11,17-oxide (**7**) is reported. Stereochemical assignments have been made on the basis of PMR (400 MHz), BB proton decoupled, SFORD, DEPT and selective heteronuclear spin decoupling ^{13}C NMR experiments. The effect of cyclisation involving 17—OH group on *in vitro* receptor binding affinity to estradiol receptors and estrogenicity in rats (*in vivo*) have also been evaluated.

In search for a typical estrogens as fertility regulating agents, a number of C-secoestradiol derivatives§ were synthesized in this laboratory[1-3]. During the course of this work, it was observed that 9,11-secoestranes having a hydroxyl group at C-11 or a 11-oic acid tend to cyclise at C-17 giving the 11,17-oxides. These unusual cyclisations, their stereochemistry and effect on estrogenicity are reported here.

Thus, 3-methoxy-11-oxo-9, 11-secoestrane-11, 17-oxide (**2**)[2] was obtained in 12-75% yields when 17β-hydroxy-3-methoxy-9,11-secoestra-1,3,5(10)-trien-11-oic acids (**1**[4]; R = R′ = H/R = H, R′—$COCH_3$/R = H, R′—THP/R = R′ = THP) were heated to 200°C in quinoline in the presence of Cu catalyst. Reduction of with borane-dimethyl sulfide complex led to 3-methoxy-9, 11-secoestrane-11, 17-oxide (**3**) in quantitative yield.

Lithium aluminium hydride reduction of the methyl ester of **1** (R = CH_3, R′ = H) resulted in 11-hydroxy-9, 11-seco-17β-estradiol 3-methyl ether (**9**). Whereas similar reduction of **2** led to the corresponding 17α-isomer (**10**).

In an attempted mesylation of 11-hydroxy-11-methyl-9, 11-seco-17β-estradiol 3-methyl-17-(tetrahydro-2H-pyran-2-yl)ether (**4**), which was prepared from **1** (R = H, R′ = THP), a facile cyclisation at C-17 led to the formation of 11-methyl-9, 11-secoestrane-11, 17-oxide (**5**)[1] in 88% yield.

A similar cyclisation at C-17 was observed when 11-hydroxy-11, 11-dimethyl-9, 11-seco-17β-estradiol 3-methyl ether 17-acetate (**6**), obtained by reaction of **1** (R = CH_3, R′ = H) with the Grignard reagent, CH_3MgI in ether-THF, was refluxed in dry benzene in the presence of catalytic amount of p-toluenesulfonic acid. The product was a mixture of two compounds, which were separated by column chromatography and characterised as 3-methoxy-11, 11-dimethyl-9, 11-secoestrane-11, 17-oxide (**7**) (50% yield) and 17β-acetoxy-3-methoxy-11-methyl-11-methylene-9, 11-secoestra-1, 3, 5(10)-triene (**8**) (38% yield).

Dreiding models of 9, 11-secoestradiol derivatives suggest that only *cis* fusion is possible in cyclopenta(b) furan ring formation. This would require α-oriented chain at C-13 to cyclise at C-17 only from α-side (cf Dygos and Chinn[5]).

Involvement of C-17 position in the cyclisation was obvious from the CMR studies using distortionless enhancement by polarisation transfer (DEPT)[6] techniques in which primary, secondary, tertiary and quaternary carbon atoms could be clearly distinguished. CMR data of compounds **2, 3, 6, 7, 9** and **10** are given in Table 1.

A change in the stereochemistry at C-17, on cyclization has been proved by lithium aluminium hydride reduction of **1** (R = CH_3, R′ = H) and **2** which led to two isomeric alcohols **9** and **10** respectively as was evident from a downfield shift of 7 ppm of C-18 (angular methyl) in **10** as compared to the corresponding 17β-hydroxy compound **9**, which has an established stereochemistry. An upfield shift of 4.3 ppm of C-12 (methylene) in **10** further supported its 17α-hydroxy stereochemistry.

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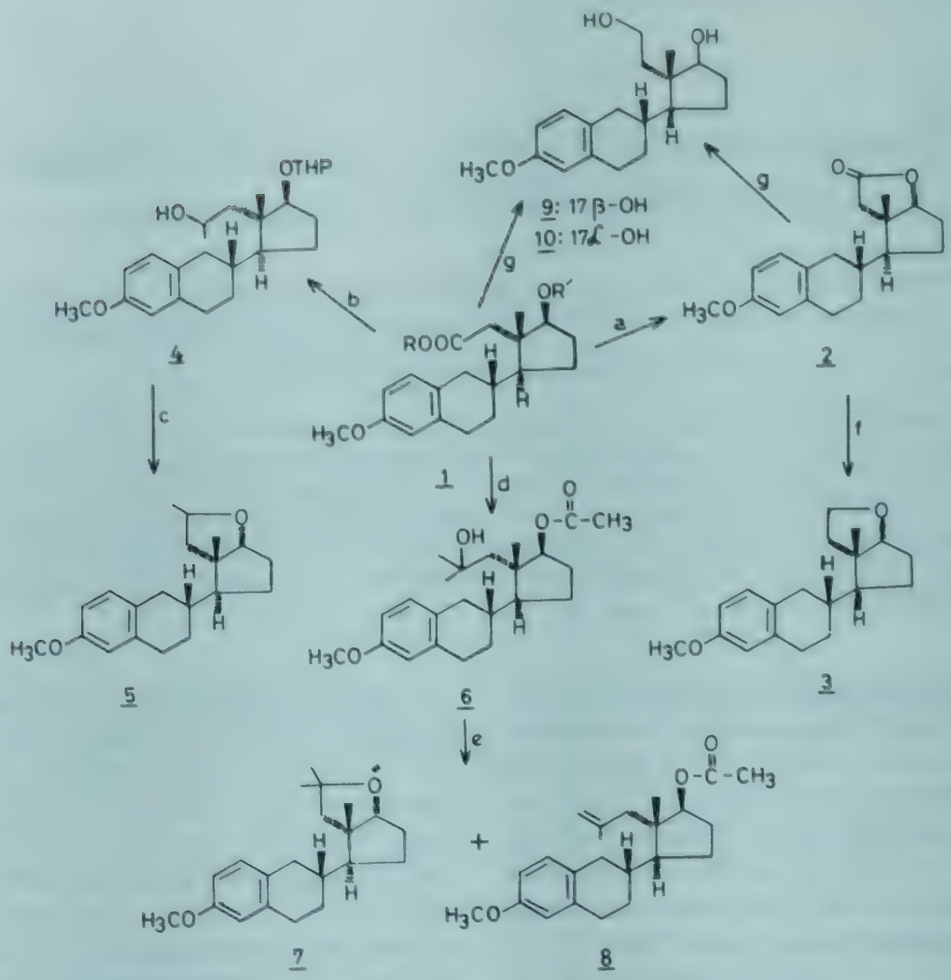
§ Secoesteroid nomenclature and numbering has been retained in these oxides for the ease of discussion instead of naming them as cyclopenta(b) furans, e.g. compound **2** as hexahydro-3a-methyl-2-oxo-4-(1′, 2′, 3′, 4′-tetrahydro-6′-methoxy-2′-napthalenyl)-2H-cyclopenta(b) furan.



a: Cu; quinoline; Δ.
b: CH_3Li; LAH.
c: Pyridine; Ms Cl.
d: CH_3MgI.
e: PTSA; C_6H_6.
f: $BH_3-(CH_3)_2S$ Complex.
g: LAH

The stereochemistry of **3** would be the same as that of **2** as it was obtained by the stereoselective reduction of **3** by borane-dimethyl sulfide complex. The shift positions of C-12 in compounds **2, 3, 6, 7, 9** and **10** which were significantly downfield were in accordance with the substitution effect at C-11[7]. The identity of C-12 methylene was confirmed by low power specific proton decoupling ^{13}C NMR experiments with **2, 6** and **7** which resulted in an enhancement of the C-12 resonance on irradiating the corresponding methylene proton frequency.

The change in stereochemistry at C-17 during cyclisation would suggest elimination of the 17β-hydroxy group. In the formation of the lactone (**2**), it is likely that the carbonium ion generated at C-17 is attacked by the carboxyl anion. A similar course of reaction can be visualised for the formation of **5** involving attack by a secondary alcohol. However, formation of the dimethyl oxide (**7**) from a tertiary alcohol is rather intriguing; no definite mechanism could be suggested for its formation. A similar situation has been reported by Dygos and Chinn[5].

Experimental Procedure

Melting points were taken in a sulphuric acid bath and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 157 spectrophotometer (ν max in cm^{-1}), and high resolution PMR (400 MHz) and CMR spectra on a BRUKER WM-400 superconductive FT NMR spectrometer equipped with ASPECT-2000 computer using the DIS NMR programme version 85010.0. TMS was used as reference. The ^{13}C-broad band (BB), SFORD, DEPT and specific proton decoupled ^{13}C NMR spectra were obtained using low decoupler power (2 watt) in CW mode. Mass spectra were taken on a JEOL-JMS D300 instrument operating at 70 eV.

3-*Methoxy*-9, 11-*secoestrane*-11,17-*oxide* (**3**)

A mixture of **2** (0.05 g, 0.00017 mol) and borane-dimethyl sulfide complex (in excess) was kept overnight at room temperature. The reaction mixture was decomposed with saturated aq ammonium chloride and extracted with ether, the organic extract washed with water, dried (Na_2SO_4) and concentrated. The

Table 1—Carbon-13 Chemical Shifts (δ_C)[a] of **2, 3, 6, 7, 9** and **10**

Carbon No.	2		3		6		7		9		10	
	δ_C	S[b]	δ_C	S[b]	δ_C	S[b]	δ_C	S[b]	δ_C	S[b]	δ_C	S[b]
1	129.8 *d*	+	129.9 *d*	+	129.8 *d*	+	129.9 *d*	+	129.9 *d*	+	129.9 *d*	+
2	113.6 *d*	+	113.5 *d*	+	113.4 *d*	+	113.5 *d*	+	113.4 *d*	+	113.3 *d*	+
3	157.9 *s*	+	157.7 *s*	+	157.7 *s*	+	157.6 *s*	+	157.7 *s*	+	157.5 *s*	+
4	112.1 *d*	+	111.9 *d*	+	111.9 *d*	+	111.4 *d*	+	111.9 *d*	+	111.8 *d*	+
5	137.3 *s*	+	137.7 *s*	+	137.7 *s*	+	137.8 *s*	+	137.8 *s*	+	137.8 *s*	+
6	29.0 *t*	−	30.0 *t*	−	28.4 *t*	−	29.2 *t*	−	29.0 *t*	−	29.8 *t*	−
7	27.4 *t*	−	28.9 *t*	−	27.7 *t*	−	27.4 *t*	−	27.8 *t*	−	28.7 *t*	−
8	35.8 *d*	+	35.7 *d*	+	34.4 *d*	+	36.7 *d*	+	36.1 *d*	+	35.9 *d*	+
9	34.8 *t*	−	34.9 *t*	−	36.5 *t*	−	34.4 *t*	−	36.3 *t*	−	36.1 *t*	−
10	127.5 *s*	+	128.5 *s*	+	128.9 *s*	+	128.5 *s*	+	128.9 *s*	+	128.9 *s*	+
11	176.4 *s*	+	68.3 *t*	−	71.7 *s*	+	89.0 *s*	+	59.5 *t*	−	59.2 *t*	−
12	43.4 *t*	−	41.4 *t*	−	52.6 *t*	−	50.4 *t*	−	43.4 *t*	−	39.1 *t*	−
13	48.0 *s*	+	51.5 *s*	+	47.0 *s*	+	52.1 *s*	+	46.1 *s*	+	48.4 *s*	+
14	51.0 *d*	+	51.6 *d*	+	51.7 *d*	+	47.0 *d*	+	50.9 *d*	+	50.4 *d*	+
15	21.8 *t*	−	28.4 *t*	−	23.2 *t*	−	21.8 *t*	−	23.7 *t*	−	26.1 *t*	−
16	29.5 *t*	−	30.4 *t*	−	29.6 *t*	−	31.4 *t*	−	29.8 *t*	−	30.4 *t*	−
17	93.2 *d*	+	93.7 *d*	+	81.0 *d*	+	88.3 *d*	+	80.1 *d*	+	81.4 *d*	+
18	18.9 *q*	+	20.0 *q*	+	16.0 *q*	+	14.8 *q*	+	11.2 *q*	+	18.2 *q*	+
OCH_3	55.2 *q*	+	55.2 *q*	+	55.2 *q*	+	55.2 *q*	+	55.2 *q*	+	55.2 *q*	+
					31.6 *q* (ax.)	+	29.8 *q* (ax.)	+				
					32.6 *q* (eq.)	+	30.2 *q* (eq.)	+				
					170.8 *s*	+						
					21.1 *q*	+						

(a) Multiplicity from SFORD ^{13}C NMR spectrum; (b) sign of the signal in ^{13}C DEPT spectrum

solid obtained was crystallised with hexane-benzene to give **3** (0.04 g, 100%), m.p. 77-79°; IR(KBr): 1600, 1570, 1500; PMR($CDCl_3$): δ1.08 (*s*, 3H, 18-C*H*$_3$), 1.32-2.14 (*m*, 10H, C—7, 8, 14, 15, 16 protons), 2.44-2.52 (*dd*, 1H, 9-CH_2, *J*= 8Hz), 2.74-2.90 [*m*, 3H, 6—CH_2 & 9—CH_2 (one H)], 3.8 (*s*, 3H, 3—OCH_3), 3.84-4.02 (*m*, 3H, 17—CH & 11—CH_2(, 6.56-7.02 (m, 3H, Ar-*H*), MS: *m/z* 286 (M^+) (Found C, 79.5, H, 8.9. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.0%).

3-Methoxy-11, 11-dimethyl-9, 11-secoestrane-11, 17-oxide (**7**) *and 17β-acetoxy-3-methoxy-11-methyl-11-methylene-9, 11-secoestra-1, 3, 5-triene* (**8**)

A mixture of **6** (0.80 g, 2.14 mmol) and PTSA (0.02 g, 0.12 m mol) in anhydrous benzene (30 ml) was refluxed for 2 hr. Reaction mixture was successively washed with Na_2CO_3 and water, dried (Na_2SO_4) and the solvent distilled off. Product thus obtained was chromatographed over silica gel. Benzenehexane (1:1) eluates yielded **8** as a syrup, yield 0.282 g (38%); IR (neat): 1720 (17—$OCOCH_3$), 1640(C = CH_2), 1600, 1580, 1500 (aromatic); PMR(CCl_4):δ0.90 (*s*, 3H, 18—CH_3), 1.58(*s*, 2H, C-12 protons), 1.68 (*s*, 3H, 11-CH_3), 2.07 (*s*, 3H, 17—$OCOCH_3$), 2.63 (*m*, 4H, C-6 & C-9 protons), 3.58 (*s*, 3H, 3-O*CH*$_3$), 4.57 (2*s*, 2H, 11-CH_2), 4.75 (*m*, 1H, 17-H), 6.25-6.78 (*m*, 3H, Ar-H); MS: *m/z* 356 (M^+) (Found: C, 77.6; H, 9.4. $C_{23}H_{32}O_3$ requires C, 77.4; H, 9.0%).

Benzene eluates yielded **7**, which was crystallised from methanol; yield 0.34 g (50%); m.p. 131-32°; IR(KBr): 1600, 1580, 1500; PMR($CDCl_3$): δ0.90 (*s*, 3H, 18-CH_3), 1.34 and 1.44 (2*s*, 6H, 2 × -CH_3, *gem*-dimethyls), 2.68-2.88 (*m*, 4H, 6 & 9-CH_2), 3.70-3.82 (*m*, 4H, 3-OCH_3 & 17-CH), 6.60-7.0 (*m*, 3H, Ar-H); MS: *m/z* 314 (M^+) (Found: C, 79.9; H, 9.3. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%).

Biological activity

Compounds **2, 3, 5, 7, 9** and **10** did not show any affinity for 17β-estradiol receptor and were devoid of uterotrophic activity (100 μg × 3 days) in rats. As the 17β-hydroxy group in estradiol is essential for receptor binding and subsequent estrogenicity, conversion of the 17β-hydroxy group in 9,11-secoestradiols to the corresponding 11,17-oxides could be a likely reason for the loss in biological activity[8].

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Synthesis of (±)-7,8- & 5,6-Dimethyl-2-(2-hydroxyisopropyl) tetralins, Stress Metabolites from Tobacco Mosaic Virus Infested Tobacco†

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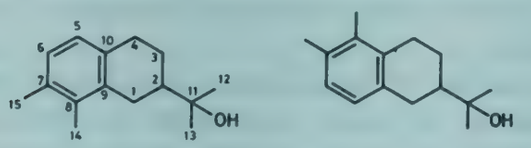
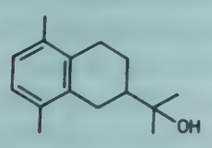
Two stress metabolites (**1** and **2**) produced by tobacco leaves inoculated with tobacco mosaic virus have been synthesized from the tetrahydronaphthoates (**9** and **10**), elaborated in turn from 2,3-dimethylbenzaldehyde (**6**) and 4-(2,3-dimethylphenyl)butanoic acid (**12**) respectively.

The two isomers of occidol (**3**) isolated[1] recently along with **3** as stress metabolites[2] from tobacco leaves (*Nicotiana rustica*) inoculated with tobacco mosaic virus (TMV), were assigned the structures on 7,8-dimethyl-(**1**)- and 5,6-dimethyl-(**2**)-2-(2-hydroxyisopropyl) tetralins. Many syntheses of **3**[3] are available, including one from our laboratory[3h]. The tetralins (**1**) and (**3**) were isolated from the natural source as a mixture which was separated with difficulty and the structure deduction of **1** largely rested on the spectral data of the mixture[1]. It therefore appeared worthwhile to undertake the synthesis of **1** and **2** and in this paper is described their first unambiguous synthesis.



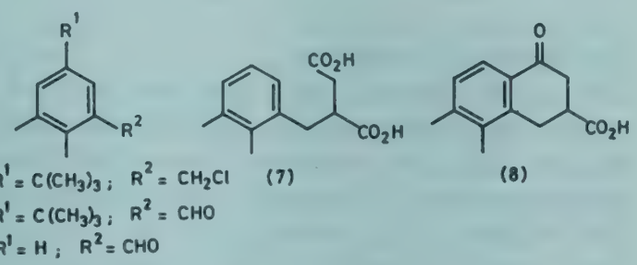
(1)

(2)

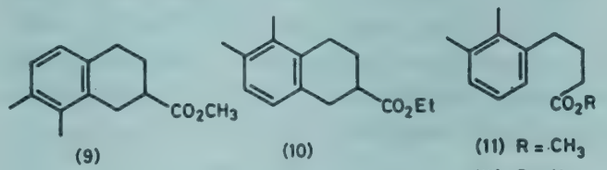


(3)

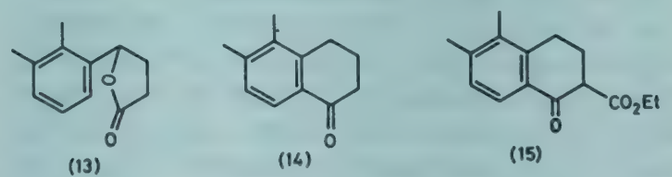
2,3-Dimethylbenzaldehyde[4] (**6**), the starting material for the synthesis of**1**, was prepared in a better overall yield from the known 5-*t*-butyl-2,3-dimethylbenzyl chloride[5] (**4**) which gave **5** on Sommelet reaction[4b] and **6** on further de-*t*-butylation[6]. Elaboration of **6** to (2,3-dimethylbenzyl)succinic acid (**7**) was achieved essentially following the procedure of Katsui *et al.*[7], i.e., via Stobbe condensation and reduction. Cyclodehydration of **7** with polyphosphoric acid furnished



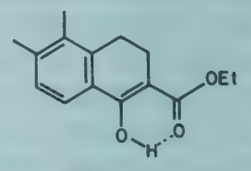
(4) $R^1 = C(CH_3)_3$; $R^2 = CH_2Cl$ (7) (8)
(5) $R^1 = C(CH_3)_3$; $R^2 = CHO$
(6) $R^1 = H$; $R^2 = CHO$



(9) (10) (11) R = CH_3
(12) R = H



(13) (14) (15)



(16)

the required tetralonecarboxylic acid (**8**). That only the terminal primary carboxyl, and not the secondary, is involved in the cyclodehydration has been well established in an analogous case[8]. Clemmensen reduction[9] of **8** followed by esterification gave the tetrahydronaphthoate (**9**) which on Grignard reaction with methylmagnesium iodide gave the stress metabolite (**1**), identical (PMR and ^{13}CNMR) with the natural product[1].

The tetrahydronaphthoate analogue (**10**) or **9**, required for the synthesis of **2** was secured from the known[10] tetralone (**14**), which in turn was obtained via the arylbutanoate[6] (**11**) by cyclodehydration of the corresponding acid (**12**) with 80%

†Part LXX in the series, Studies in Terpenoids. Part LXIX, Murali D & Krishna Rao G S, *Indian J Chem*, **26B** (1987) 158.

sulphuric acid. An attempt to make use of the unsaturated half-ester acid precursor of **7**, obtained during the Stobbe condensation of **6**, for the preparation of **12**, by the reported decarboxylative lactonization procedure[11], gave a poor yield (12%) of the expected lactone (**13**) which on hydrogenolysis would give **12**. Carbethoxylation[12] of **14** in benzene (no reaction in ether[13]) gave the β-keto ester (**15**, which existed predominantly (−60%) in the enolic form (**16**). Modified Clemmensen reduction[14] of the tetralone ester (**15**) gave the tetrahydronaphthoate (**10**) which on Grignard reaction with methylmagneisum iodide gave **2**, identical with the natural product[1] (PMR and ^{13}CNMR).

Experimental Procedure

M.ps (uncorrected) were determined using Kofler hot stage apparatus. B.t. refers to bath temperature at which the compound was sublimed under reduced pressure. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer (ν_{max} in cm^{-1}) and PMR and ^{13}CNMR spectra on Varian T-60 (at 60 MHz) and Jeol FX-90Q (at 22.5 MHz) spectrometers respectively, using TMS as internal standard (chemical shifts in δ ppm). Pet. ether refers to the fraction, b.p. 60-80°.

5-t-Butyl-2,3-dimethylbenzaldehyde (**5**)

A mixture of **4**[5] (105.5 g, 0.5 mol), hexamethylenetetramine (280 g, 2.0 mol) and 50% aq.HOAc (875 ml) was heated under reflux for 6 hr. Conc. HCl (350 ml) was added to the reaction mixture and heating continued for another 2 hr. After cooling, the organic layer was separated and the aqueous layer, after dilution with water (1 litre), was extracted with ether (150 ml × 5). The combined organic phase was washed successively with water (100 ml × 3), saturated aq. $NaHCO_3$ (100 ml), water (100 ml) and dried (Na_2SO_4). The residue obtained after solvent removal was subjected to fractional distillation and the fraction collected at 135-50°/4 mm was redistilled (b.p. 137-40°/4 mm) to give **5** (55 g, 58.6%) which solidified on standing, m.p. 58° (from pet. ether); IR (nujol): 2820, 2750, 1700, 1605, 1575; PMR (CCl_4): 1.35 [9H, *s*, $C(CH_3)_3$], 2.32 (3H, *s*, $ArCH_3$), 2.5 (3H, *s*, $ArCH_3$), 7.28 (1H, *d*, *J*=2 Hz, ArH_4), 7.55 (1H, *d*,*J*=2 Hz, ArH_6), and 10.2 (1H, *s*, CHO) (Found: C, 82.3; H, 9.3. $C_{13}H_{18}O$ requires C, 82.1; H, 9.5%).

(2,3-Dimethylbenzyl)succinic acid (**7**)

A mixture of **5** (53.5 g, 0.282 mol), anhyd. $AlCl_3$ (60 g, 0.45 mol) and dry benzene (600 ml) was stirred at room temperature for 48 hr, and therefore decomposed by pouring it into conc. HCl (100 ml) containing ice (300 g). Benzene layer was separated and aqueous layer extracted with ether (75 ml). The combined organic phase was washed successively with water (150 ml × 2), saturated aq.$NaHCO_3$ (150 ml), and water (150 ml) and dried (Na_2SO_4). After removal of solvent, the residue was fractionated and the fraction distilling at 105-15°/15 mm was redistilled (b.p. 108-10°/15 mm; lit.[4] b.p. 90°/13 mm) to give **6**[4](24.5 g, 65%).

To a solution of *t*-BuOK [prepared from *t*-BuOH (50 ml) and potassium (1.6 g, 0.04 g atom)] was added, with stirring under nitrogen blanket, a mixture of **6** (4 g, 30 mmol) and diethyl succinate (11.68 g, 80 mmol), in one lot. After 8 hr of refluxing, *t*-BuOH was removed under reduced pressure. Dil. HCl (2*N*, 25 ml) was added to the cooled reaction mixture and the product extracted with 10% aq. Na_2CO_3 (50 ml × 3), the alkaline phase acidified with 1:1 HCl and extracted with ether (75 ml × 3). The ether extract after washing with brine (75 ml) was dried (Na_2SO_4). The gummy half-ester acid (7 g, 89.5%), obtained after solvent removal was used as such in the next reaction.

A solution of the half-ester acid (7 g) in 10% aq. NaOH (300 ml) was heated at 100° (water-bath) for 3 hr. To the cooled solution, Ni-Al alloy (1:1) (30 g) was added slowly such that the reaction remained under control. The reduction was completed by heating the reaction mixture on the water-bath for 8 hr. The residual nickel was filtered off and the filtrate acidified with 1:1 HCl. The precipitated white solid was recovered by filtration and air-dired to give **7** (5 g, 79.3%), m.p. 182° (from water); IR (nujol): 3400-2400 (broad), 1710, 1700, 785; PMR (DMSO-d_6 + $CDCl_3$) 2.22 (3H, *s*, $ArCH_3$), 2.25 (3H, *s*, $ArCH_3$), 2.33-3.27 (5H, *m*, $ArCH_2CHCH_2$), and 6.93 (3H, *s*, ArH_4, H_5 and H_6) (Found: C, 66.1; H, 6.8. $C_{13}H_{16}O_4$ requires C, 66.4; H, 6.8%).

5,6-Dimethyl-1-tetralone-3-carboxylic acid (**8**)

The dicarboxylic acid (**7**) (2 g) was stirred with PPA [prepared from P_2O_5 (50 g) and orthophosphoric acid (30 ml)], at 95° for 3 hr. The dark-brown reaction mixture was poured onto crushed ice (75 g). The product was extracted with ether (75 ml × 3) and the combined ethereal layer washed with water (75 ml) and re-extracted with 10% aq. Na_2CO_3 (75 ml × 3). The alkaline solution was acidified with 1:1 HCl. The precipitated grey solid was chromatographed over a silica gel column ($CHCl_3$-benzene) to give colourless

prisms of **8** (1.4 g, 75.8%), m.p. 170° (from $CHCl_3$-benzene); IR (nujol): 3200, 1730, 1660, 1595, 1570; PMR ($CDCl_3$):2.25 (3H, *s*, $ArCH_3$), 2.35 (3H, *s*, $ArCH_3$), 2.5-3.6 (5H, *m*, $ArCH_2CHCH_2$), 7.1 (1H, *d*,J=8 Hz, ArH_7), and 7.82 (1H, *d*,J=8 Hz, ArH_8) (Found: C, 71.5; H , 6.5. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%).

Methyl 7, 8-*dimethyl*-1, 2, 3, 4-*tetrahydro*-2-*naphthoate* (**9**)

A mixture of **8** (1.4 g), amalgamated Zn (prepared from 12 g of Zn granules), conc. HCl (18 ml), water (7.5 ml), and toluene (15 ml) was heated to reflux for 36 hr during which a 5 ml portion of conc. HCl was added every 6 hr. The product after usual work up gave 7,8-dimethyl-1,2,3,4-tetrahydro-2-naphthoic acid (1.2 g, 91.6%), which was used directly in the esterification step; IR (nujol): 3400-2300 (broad), 1700; PMR ($CDCl_3$ + DMSO-d_6):2.12 (3H, *s*, $ArCH_3$), 2.23 (3H, *s*, $ArCH_3$), 1.5-3.23 [7H, *m*, $CH_2CH(CH_2)_2$], 6.82 (2H, merged ABq, J=9 Hz, ArH_5 and H_6), and 7.1 (1H, *bs*, COOH).

A mixture of the above tetrahydronaphthoic acid (1 g, 5.0 mmol), dimethyl sulphate (0.76 g, 6.0 mmol), anhyd. K_2CO_3 (2 g) and dry acetone (20 ml) was stirred under reflux for 20 hr. Most of the acetone was distilled off, water (50 ml) added to the residue and the product extracted with ether (30 ml × 3). The combined ether extract after usual work-up gave **9** which was purified by preparative TLC [silica gel, pet. ether-benzene (1:1)], b.t. 140-45°/1 mm; IR (neat): 1735, 1170; PMR (CCl_4): 2.10 (3H, *s*, $ArCH_3$), 2.18 (3H, *s*, $ArCH_3$), 1.40-3.0 [7H, *m*, $CH_2CH(CH_2)_2$], 3.68 (3H, *s*, CO_2CH_3), and 6.8 (2H, merged ABq, J=9 Hz, ArH_5 and H_6) (Found: C, 76.8; H, 8.5. $C_{14}H_{18}O_2$ requires C, 77,0; H, 8.3%).

(±)-7,8-*Dimethyl*-2-(2-*hydroxyisopropyl*) *tetralin* (**1**)

The ester (**9**) (0.6 g, 2.75 mmol) in dry ether (10 ml) was added dropwise to a solution of MeMgI [prepared from Mg (0.73 g, 0.03 g atom) and MeI (5.62 g, 40 mmol)] in ether (30 ml). The mixture was stirred overnight and heated to reflux for 1 hr. Saturated aq. NH_4Cl (50 ml) was added slowly to the cooled (ice-salt bath) reaction mixture. The product after usual work-up, followed by purification by preparative TLC [silica gel, $CHCl_3$-benzene (3:2)], gave analytically pure **1** as a colourless oil (0.55 g, 91.7%); IR (CCl_4): 3620; PMR (CCl_4): 1.2 [6H, *s*, C $(CH_3)_2$], 1.00-2.83 [7H, *m*, $CH_2CH(CH_2)_2$], 2.07 (3H, *s*, $ArCH_3$), 2.18 (3H, *s*, $ArCH_3$), 6.65 (2H, merged ABq, J=8 Hz, ArH_5 and H_6); ^{13}CNMR ($CDCl_3$): 134.8 (*s*, C-7 and C-8), 134.2 (*s*, C-9 or C-10), 133.5 (*s*, C-10 or C-9), 127.0 (*d*, C-5 or C-6), 125.9 (*d*, C-6 or C-5), 72.8 (*s*, C-11), 46.2 (*d*, C-2), 30.7 (q, C-4), 28.9 (*t*, C-1), 27.1 (q, C-12 or C-13), 26.6 (*q*, C-13 or C-12), 23.9 (*t*, C-3), 20.4 (*q*, C-15), and 14.8 (*q*, C-14) (for assignments, see ref. 1) (Found: C 82.2; H, 10.4. Calc for $C_{15}H_{22}O$: C, 82.5; H, 10.2%).

Ethyl 5, 6-*dimethyl*-1, 2, 3, 4-*tetrahydro*-2-*naphthoate* (**10**)

A solution of **14**[10] (0.85 g, 4.9 mmol) in dry benzene (20 ml) was slowly added (~1 hr) under stirring to a mixture of NaH (0.375 g, 15.6 mmol) and diethyl carbonate (4.5 g, 3.8 mmol) in refluxing benzene (30 ml). Refluxing was continued for another 10 hr. After cooling the reaction mixture in ice-salt bath, excess NaH was decomposed, the precipitated solid dissolved in water and the organic layer separated. Usual work-up gave **15** as a mixture along with its tautomer (**16**) (**15**:**16**, 2:3), as indicated by IR and PMR spectra; yield 1.1 g (91.5%); IR (neat): 3600-2300 (br, enol OH), 1740 (*CO*OEt of keto form), 1690 (Ar*CO* of keto form), 1645 (*CO*OEt of enol form), 1615 (C=C of enol form), 1595, 1565; PMR (CCl_4):(i) peaks corresponding to **15**:1.25 (*t*,J=7 Hz, CH_2CH_3), 3.27 (*t*,J=7 Hz,$CHCO_2Et$), 4.13 (*q*,J=7 Hz, CH_2CH_3), 6.95 (*d*,J=8 Hz, ArH_7), and 7.67 (*d*,J=8 Hz, ArH_8); (ii) peaks corresponding to **16**: 1.32 (*t*,J=7 Hz, CH_2CH_3), 4.2 (*q*,J=7 Hz, CH_2CH_3), 6.92 (*d*,J=8 Hz, ArH_7), 7.47 (*d*,J=8 Hz, ArH_8), and 12.35 (*s*, C=C-OH); (iii) peaks common to **15** and **16**: 2.15 (3H, *s*, $ArCH_3$), 2.27 (3H, *s*, $ArCH_3$), and 1.67-2.93 (4H, *m*, CH_2CH_2).

To a solution of **15** (0.5 g) in dry ether (125 ml) presaturated with dry HCl gas at 0°, activated zinc dust[14] (5 g) was slowly added under vigorous stirring, maintaining the temperature below 5° (ice-salt bath). The reaction mixture was stirred for additional 3 hr at 0° and poured into ice-water (250 ml). The product was worked-up with ether and the crude product purified by preparative TLC [silica gel, pet. ether-benzene (1:1)] to give **10** (0.3 g, 63.6%), b.t. 140-45°/1 mm; IR (neat): 1735; PMR (CCl_4): 1.27 (3H, *t*,J=7 Hz, CH_2CH_3), 1.46-3.0 (7H, *m*, $CH_2CH_2CHCH_2$), 2.05 (3H, *s*, $ArCH_3$), 2.18 (3H, *s*, $ArCH_3$), 4.07 (2H, *q*, J=7 Hz, CH_2CH_3), and 6.71 (2H, merged AB*q*,J=8 Hz, ArH_7 and H_8) (Found: C, 77.2; H, 8.8. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.7%).

(±)-5,6-*Dimethyl*-2-(2-*hydroxyisopropyl*)*tetralin* (**2**)

A solution of **10** (0.2 g, 0.862 mmol) in dry ether (10 ml) was added dropwise under stirring

to a mixture of MeMgI [prepared from Mg (0.22 g, 0.009 g atom) and MeI (1.42 g, 10.0 mmol) in dry ether (25 ml)]. The mixture was boiled under reflux for 10 hr, cooled in ice-salt bath and decomposed by the slow addition of saturated aq. NH_4Cl (25 ml). The ether layer was separated and the aqueous phase extracted with ether (20 ml × 3). The combined ethereal layer after usual work-up, followed by preparative TLC [silica gel, $CHCl_3$-benzene (3:2)] of the crude product gave crystalline **2** (0.16 g, 85%), m.p. 77.5° (from $CHCl_3$-pet. ether); IR (CCl_4): 3620; PMR (CCl_4): 1.17 [6H, *s*, $C(CH_3)_2$], 1.0-2.9 [8H, *m*, $CH_2CH(CH_2)_2$ and OH], 2.03 (3H, *s*, $ArCH_3$), 2.17 (3H, *s*, $ArCH_3$), and 6.65 (2*H*, merged Ab*q*,*J*=9 Hz, ArH_7 and H_8); ^{13}CNMR ($CDCl_3$):134.7 (*s*, C-5 or C-6), 134.2 (*s*, C-9 or C-10 and C-6 or C-5), 133.2 (*s*, C-10 or C-9), 127.0 (*d*, C-7 or C-8), 126.5 (*d*, C-7 or C-8), 72.3 (*s*, C-11), 45.1 (*d*, C-2), 31.4 (*t*, C-1), 28.0 (*t*, C-4), 27.0 (q, C-12 or C-13), 26.2 (*q*, C-13 or C-12), 24.6 (*t*, C-3), 20.2 (q, C-15), and 14.7 (*g*, C-14) (for assignments, see ref. 1). (Found: C, 82.4; H, 10.1. Calc for $C_{15}H_{22}O$: C, 82.5; H, 10.2%).

γ-(2,3-Dimethylphenyl)-γ-butyrolactone (**13**)

A solution of unsaturated half-ester acid (obtained from the Stobbe condensation of **6** with diethyl succinate) in HOAc (25 ml), 48% HBr (20 ml) and water (5 ml) was boiled under reflux for 6 hr. The acids (HBr and HOAc) were removed under reduced pressure. The residual oil was taken up in ether, washed with water (75 ml × 2), 10% aq. Na_2CO_3 (75 ml), followed by brine (75 ml) and dried (Na_2SO_4). Evaporation of ether gave **13** (0.45 g, 12.4%) which solidified on standing, m.p. 80°)from $CHCl_3$-pet. ether); IR(nujol): 1770; PMR (CCl_4): 1.8-2.8 (4H, *m*, CH_2CH_2), 2.13 (3H, *s*, $ArCH_3$), 2.23 (3H, *s*, $ArCH_3$), 5.6 (1H, *m*, ArC*H*), and 6.92-7.2 (3H, *m*, ArH_4, H_5 and H_6), (Found: C, 75.4; H, 7.7. $C_{12}H_{14}O_2$ requires C, 75.8; H, 7.4%).

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Studies in Nucleosides: Part XVI—Synthesis of Azathioprine Analogues†

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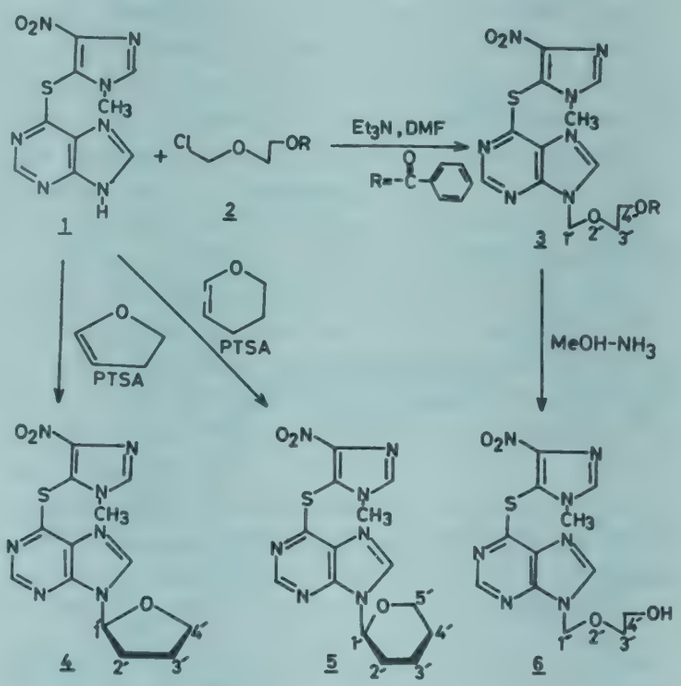
6-[(1-Methyl-4-nitroimidazo-5-yl)thio]-9-(1′-tetrahydrofuranyl)purine (**4**), 6-[(1-methyl-4-nitroimidazo-5-yl)thio]-9-(1′-tetrahydropyranyl)pyrine (**5**), 9-hydroxyethoxymethyl-6-[(1-methyl-4-nitroimidazo-5-yl)thio]purine (**6**), 6-[(1-methyl-4-nitroimidazo-5-yl)thio]-9-(β-D-ribofuranosyl)purine (**12**), 9-(α-D-arabinofuranosyl)-6-[(1-methyl-4-nitroimidazo-5-yl)thio]purine (**16**) and 9-(β-D-2′-deoxyribofuranosyl)-6-[(1-methyl-4-nitroimidazo-5-yl)thio]purine (**11**) have been synthesised. Condensation of **1** with dihydrofuran and dihydropyran gives **4** and **5** respectively in excellent yields. The reaction of **1** separately with benzoyloxyethoxymethylene chloride (**2**), 1-O-acetylribose derivative (**7**) and 1-chloro-2-deoxyribose derivative (**9**) and of the chloromercuric complex (**13**) with 1-bromoarabinose derivative (**14**) gives the blocked nucleosides (**3, 8, 10** and **15**) respectively. Deblocking of the nucleosides with methanolic ammonia finally affords **6, 12, 11** and **16** respectively.

Azathioprine (**1**), a drug in clinical use in the transplantation of organs and also effective against transplantable tumors and chronic granulocytic leukaemia[1], is a 6-mercaptopurine derivative. The glycosides, cyclic and alicyclic analogues of (**1**) appear to have not been synthesised. There are several reports where the riboside[2], deoxyriboside and arabinoside[3] have been found more effective than the parent base. Further the cyclic and alicyclic analogues of the bases probably act as pro-drugs[3]. Prompted by these reports, it was thought worthwhile to synthesize the riboside, deoxyriboside, arabinoside, cyclic and alicyclic analogues of **1**.

Condensation of **1**[4] with 2-benzoyloxyethoxymethylene chloride in the presence of triethylamine yielded **3** as the sole product. The deblocking of **3** with methanolic ammonia at ambient temperature gave 9-(hydroxyethoxy-methyl)-6-[(1-methyl-4-nitroimidazo-5-yl)thio]purine (**6**). The acid-catalysed condensation of **1** with dihydrofuran and dihydropyran gave **4** and **5** respectively in excellent yields. (Scheme 1).



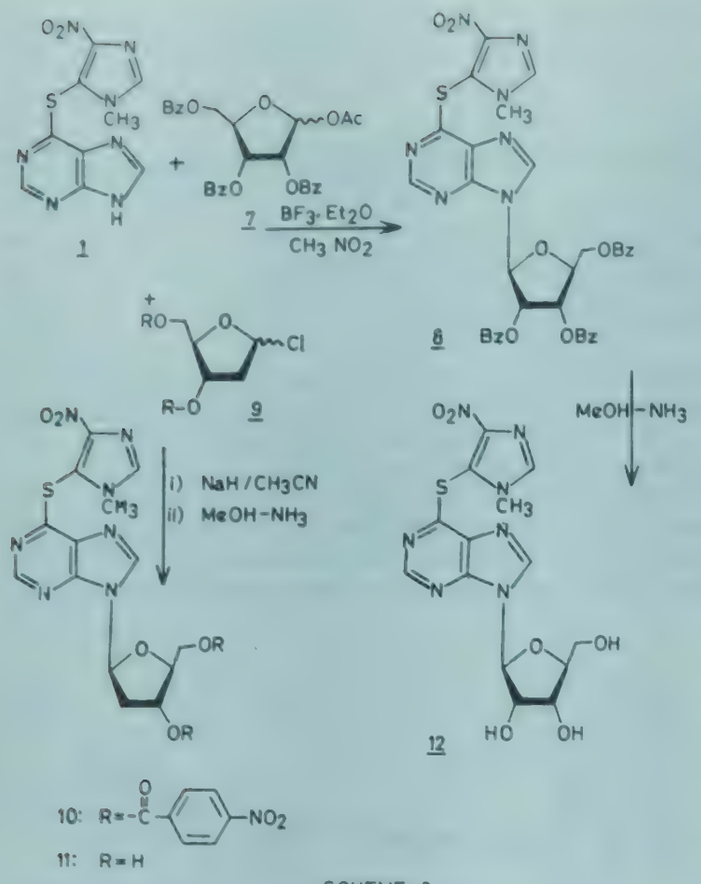
Scheme 1

Treatment of **1** with 1-O-acetyl-2, 3, 5-tri-O-benzoyl-D-ribofuranose (**7**) in the presence of $BF_3.Et_2O$ gave the protected riboside (**8**) which on deblocking with methanolic ammonia yielded 6-[(1-methyl-4-nitroimidazo-5-yl)thio]-9-(β-D-ribofuranosyl)purine (**12**) (Scheme 2). Synthesis of **12** involving several steps has been reported[5]. The present approach to **12** is much simpler. The β-configuration of **12** was evident from the coupling constant of anomeric proton (H-1′, $J_{1',2'} = 5$ Hz).

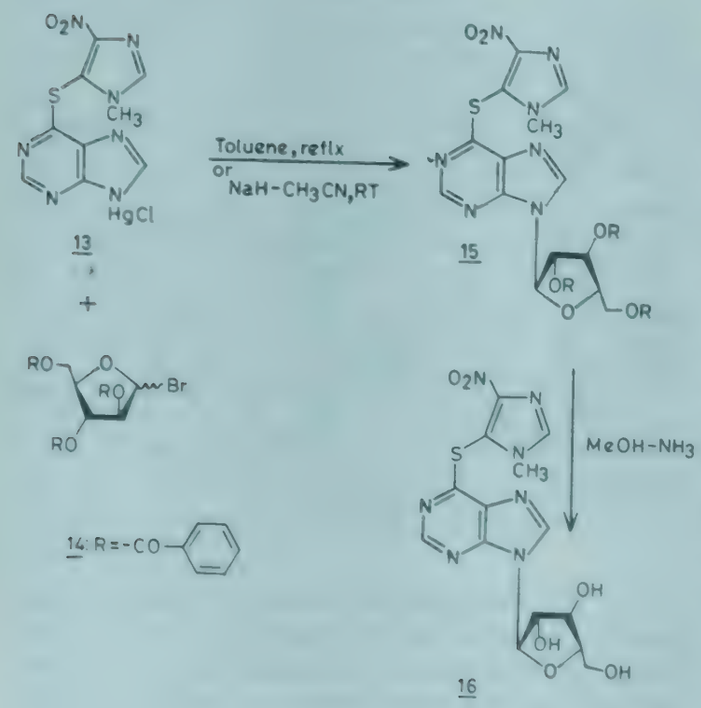
Condensation of chloromercuric complex (**13**) with 2, 3, 5-tribenzoyl-1-bromo-D-arabinose (**14**) gave the protected arabinoside (**15**) which was deblocked with methanolic ammonia in the usual way to give 6-[(1-methyl-4-nitroimidazo-5-yl)thio]-9-(α-D-arabinofuranosyl)purine (**16**) (Scheme 3). It is known that the arabinosides obtained by this procedure have α-configuration[6].

Condensation of **1** with 3, 5-di-(*p*-nitrobenzoyl)-2-deoxyribofuranosyl-1-chloride (**9**) in the presence of NaH gave, according to Robins' procedure[7], nucleoside (**10**) which on deblocking with methanolic ammonia gave 6-[(1-methyl-4-nitroimidazo-5-yl)thio]-9-(β-D-2′-deoxyribofuranosyl)purine (**11**).

† CDRI Communication No. 3952.



SCHEME 2



SCHEME 3

Experimental Procedure

For general directions see earlier papers in the series[9].

9-(Hydroxyethoxymethyl)-6-[(1-methyl-4-nitroimidazo-5-yl)thio]purine (**6**)

To a stirred mixture of **1** (0.3 g, 1 mmol), DMF (10 ml) and triethylamine (3 ml) was added dropwise a solution of benzoyloxyethoxymethylene chloride (**2**) (3g, 9.5 mmol) in DMF (5 ml) at 10-15° and the mixture further stirred at ambient temperature for 4 hr. Excess of solvent and reagent were removed under reduced pressure, the residue extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to give a crude product which was chromatographed over SiO_2 column. Elution with $CHCl_3$:MeOH (90:10, v/v) gave **3** (0.4 g, 86%), m.p. 140°; IR(KBr):1680 (C=O); PMR($CDCl_3$ + DMSO-d_6): δ8.5 (*s*, 1H, H-8), 8.35 (*s*, 1H, H-2), 8.0-7.7 (*m*, 3H, H-2 of imidazole and Ar-*H*), 7.6-7.3 (*m*, 3H, Ar-*H*), 5.7 (*s*, 2H, H-1′), 4.5-4.3 (*m*, 2H, H-3′), 4.0-3.7 (*m*, 2H, H-4′) and 3.6 (*s*, 3H, N−C*H*$_3$) (Found: C, 49.9; H, 4.0. $C_{19}H_{17}N_7O_5S$ requires C, 50.2; H, 3.7%).

A mixture of **3** (6.6 g, 1.3 mmol) and methanol (10 ml) saturated with ammonia at 0° was kept at ambient temperature for 48 hr. Excess of methanolic ammonia was removed under reduced pressure and the residue chromatographed over SiO_2 column. Elution with $CHCl_3$:MeOH (90:10, v/v) gave **6** (0.14 g, 31%), m.p. 180°; PMR($CDCl_3$ + DMSO-d_6): δ 8.5 (*s*, 1H, H-8), 8.3 (*s*, 1H, H-2), 8.0 (*s*, 1H, H-2 of imidazole), 5.8 (*s*, 2H, H-1′), 4.8 (*bs*, 1H, O*H*), 3.7 (*s*, 3H, N—C*H*$_3$), 4.0-3.4 (*m*, 4H, H-3′ and H-4′); (Found: C, 40.8; H, 4.0. $C_{12}H_{13}N_7O_4S$ requires C, 41.0; H, 3.7%).

6-[(1-Methyl-4-nitroimidazo-5-yl)thio]-9-(tetrahydrofuranyl)purine (**4**)

A mixture of **1** (1 g, 3.6 mmol), 2,3-dihydrofuran (1 g, 13.4 mmol) and *p*-toluenesulphonic acid (PTSA) (0.1 g) in ethyl acetate was stirred at 50° for 24 hr. The resulting mixture was washed with aq. K_2CO_3, water, dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue was chromatographed over SiO_2 column. Elution with $CHCl_3$:MeOH (92:8, v/v) gave **4** (1.07 g, 86%)), m.p. 151°; PMR($CDCl_3$ + DMSO-d_6): δ8.5 (*s*, 1H, H-8); 8.25 (*s*, 1H, H-2); 7.9 (*s*, 1H, H-2 of imidazole), 6.3 (*t*, 1H, H-1′, $J_{1',2'}$ = 5 Hz), 4.0 (*m*, 2H, H-4′), 3.7 (*s*, 3H, N−C*H*$_3$), 2.5-1.8 (*m*, 4H, H-2′ and H-3′) (Found: C, 44.6; H, 3.9. $C_{13}H_{13}N_7O_3S$ requires C, 45.0; H, 3.7%).

6-[(1-Methyl-4-nitroimidazo-5-yl)thio-9-(tetrahydropyranyl)purine (**5**)

This was essentially prepared by the procedure described above employing **1** (1 g, 3.6 mmol), 2, 3-dihydropyran (1 g, 11.9 mmol) and PTSA (0.1 g) work-up above gave **5** in 71% yield m.p. 163°; PMR ($CDCl_3$ + DMSO-d_6): 8.5 (*s*, 1H, H-8), 8.3 (*s*, 1H, H-2), 7.9 (*s*, 1H, H-2 of imidazole), 5.6 (*t*, 1H, H-1′, $J_{1',2'}$ = 4 Hz), 4.0-3.2 (*m*, 2H, H-5′), 3.4 (*s*, 3H, N-C*H*$_3$),

2.4-1.3 (*m*, 6H, H-2′, H-3′ and H-4′) (Found: C, 47.0; H, 4.0. $C_{14}H_{15}N_7O_3S$ requires C, 46.5; H, 4.2%).

6-[1-*Methyl*-4-*nitroimidazo*-5-*yl*)*thio*]-9-(β-D-ribofuranosyl)purine (**12**)

A mixture **1** (0.6 g, 2.1 mmol), 1-acetyl-2, 3, 5-tri-O-benzoylribofuranose (**7**) (1.2 g, 2.3 mmol) and anhyd. nitromethane (40 ml) was refluxed for 1 hr, cooled to 75°, BF_3-Et_2O (0.5 ml) added to it and again refluxed for 45 min. Excess of solvent and reagent were removed *in vacuo*, the residue extracted with ethyl acetate, washed with aq. $NaHCO_3$, dried (Na_2SO_4) and solvent removed. The oily residue was chromatographed over SiO_2 column. Elution with $CHCl_3$:MeOH (99:1, v/v) gave **8** (0.25 g, 30%), m.p. 153°; PMR ($CDCl_3$): δ 8.5 (*s*, 1H, H-8), 8.3 (*s*, 1H, H-2), 8.2-7.8 (*m*, 7H, H-2 of imidazole and Ar-*H*), 7.6-7.1 (*m*, 9H, Ar-*H*), 6.4 (*d*, 1H, H-1′, $J_{1',2'} = 4.5$ Hz), 4.8 (*m*, 5H, H-2′, H-3′ and H-4′ and H-5′), 3.6 (*s*, 3H, N − CH_3).

Deblocking of **8** was carried out as described for **3**. The crude **12** thus obtained was purified by chromatography over SiO_2 column. Elution with $CHCl_3$:MeOH (88:12, v/v) gave **12** (50%), m.p. 169° (lit.[5], 167-71°); PMR($CDCl_3$ + DMSO-d_6): 8.5 (*s*, 2H, H-2 and H-8), 7.9 (*s*, 1H, H-2 of imidazole), 6.0 (*d*, 1H, H-1′, $J_{1',2'} = 5$ Hz), 4.8-3.4 (*m*, 8H, H-2′, H-3′, H-4′, H-5′ and O*H*) 3.7 (*s*, 3H, N − CH_3).

9-(α-*D-Arabinofuranosyl*-6-[(1-*methyl*-4-*nitroimidazo*-5-*yl*)*thio*]*purine* (**16**)

Method A: A suspension of chloromercuric complex (**13**) (1.2 g, 2.3 mmol) in xylene (60 ml) was refluxed azeotropically. To it was added a solution of 2, 3, 5-tri-O-benzoyl-D-arabinofuranosyl-l-bromide (**14**) (2 g, 3.8 mmol) in xylene (20 ml). The mixture was refluxed for 4 hr filtered hot and the filter cake washed with chloroform. The solvent from the filtrate was removed *in vacuo*, the residue dissolved in chloroform, washed with 30% aq. KI, dried (Na_2SO_4) and concentrated. The oily product was chromatographed over SiO_2. Elution with $CHCl_3$:MeOH (99:1, v/v) gave the protected arabinoside (**15**), m.p. 132°; PMR($CDCl_3$):8.5 (*s*, 1H, H-8), 8.2 (*s*, 1H, H-2), 8.0-7.7 (*m*, 7H, H-2 of imidazole and Ar-*H*), 7.5-7.0 (*m*, 9H, Ar-*H*), 6.4 (*d*, 1H, H-1′, $J_{1',2'} = 2$ Hz), 5.8 (*m*, 1H, H-2′), 5.3-4.5 (*m*, 4H, H-3′, H-4′ and H-5′), 3.6 (*s*, 3H, N—CH_3) (Found: C, 57.9; H, 3.5. $C_{35}H_{27}N_7O_9S$ requires C, 58.2. H, 3.8%).

Method B: A mixture of **1** (0.95 g, 5 mmol), NaH (50% oil, 0.25 g, 6.2 mmol) and anhyd. CH_3CN (35 ml) was stirred at ambient temperature under N_2 atmosphere for 30 min. To it was added (**14**), the mixture stirred for 15 hr and the separated solid removed by filtration. The solvent from the filtrate was removed *in vacuo* and the oily residue was chromatographed over SiO_2 column. Elution with $CHCl_3$:MeOH (99:1 v/v) gave **15** (0.73 g, 55%), m.p. 135°.

Deblocking of **15** as described for **3** gave crude **16** which was chromatographed over a column of SiO_2. Elution with $CHCl_3$:MeOH (85:15, v/v) gave **16** (37%), m.p. 155°; PMR($CDCl_3$ + DMSO-d_6):8.5(*s*, 2H, H-2 and H-8), 8.0(*s*, 1H, H-2 of imidazole), 6.0 (*d*, 1H, H-1′, $J_{1',2'} = 3$ Hz), 4.7-3.3 (*m*, 8H, H-2′, H-3′, H-4′, H-5′ and O*H*) 3.6 (*s*, 3H, N—CH_3) (Found: C, 41.1; H, 3.7. $C_{14}H_{15}N_7O_6S$ requires C, 41.07; H, 3.7%).

9-(β-D-2′-*Deoxyribofuranosyl*)-6-[(1-*methyl*-4-*nitroimidazo*-5-*yl*)*thio*]*purine* (**11**)

A mixture of **1** (0.95 g, 3.4 mmol), NaH (50% oil, 0.25 g) and anhyd. CH_3CN was stirred at ambient temperature under nitrogen atmosphere for 30 min. To it was added 1-chloro-2-deoxy-3, 5-di-O-(*p*-nitrobenzoyl)ribofuranose (**9**) (1.6 g, 3.4 mmol). The mixture was stirred for 15 hr and worked up in the usual manner. The crude product was chromatographed over a column of SiO_2. Elution with $CHCl_3$:MeOH (98:2, v/v) gave the protected nucleoside (**10**) (1.2 g, 55%), m.p. 160°; PMR($CDCl_3$):8.6 (2*s*, 2H, H-2 and H-8), 8.3 (*m*, 4H, 4 Ar-*H*), 8.0 (*m*, 5H, H-2 of imidazole, Ar-*H*), 6.2 (*dd*, 1H, H-1′, $J_{1',2'} = 11$, 1.5 Hz), 5.7 (*m*, 2H, H-3′ and H-4′), 4.2 (*m*, 2H, H-5′), 3.7 (*s*, 3H, N—CH_3), 2.45 (*m*, 2H, H-2′) (Found: C, 48.3; H, 3.1. $C_{28}H_{21}N_9O_{11}S$ requires C, 48.6; H, 3.1%).

Deblocking of **10** as usual afforded crude **11** which was chromatographed over a column of SiO_2. Elution with $CHCl_3$:MeOH:CH_3COCH_3 (88;10;2, v/v) gave **11** (0.43 g, 50%), m.p. 215° (d); PMR($CDCl_3$ + DMSO-d_6):8.6(*s*, 1H, H-8), 8.5 (*s*, 1H, H-2) 8.1 (*s*, 1H, H-2 of imidazole), 6.0-5.6 (*dd*, 1H, H-1′, $J_{1',2'} = 11.2$ Hz), 4.9-4.5 (*m*, 2H, H-3′, H-4′), 4.0-3.5 (*m*, 4H, H-5′, O*H*), 3.7 (*s*, 3H, N—CH_3), 2.4-1.8 (*m*, 2H, H-2′) (Found: C, 42.5; H, 3.9. $C_{14}H_{15}N_7O_5S$ requires C, 42.7; H, 3.8%).

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Studies in Nucleosides: Part XVII—Synthesis of 4-Amino-6-methoxypyrazolo[3,4-*d*]pyrimidine & 4-Amino-6-methylthiopyrazolo[3,4-*d*]pyrimidine Ribosides & Their Antiviral Activity†

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4-Amino substituted-6-methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidines (**8** and **9**), 4-amino-6-methoxy-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**15**) and 4-amino-6-methylthio-1-(α-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**12**) have been synthesised. Condensation of 4,6-dimethylthiopyrazolo[3,4-*d*]pyrimidine (**1**) with ribofuranosyl derivative (**4**) leads to a mixture of β-isomer (**5**) and α-isomer (**6**). Deblocking of **5** and **6** with methanolic ammonia affords **10** and **11** respectively. Treatment of **10** with NH_3, CH_3NH_2 and NH_2-NH_2 leads to **7**, **8** and **9** respectively. Under similar condition treatment of **11** with NH_3 yields **12**. Acetylation of **7** followed by oxidation with $KMnO_4$ in acetic acid gives **14** which on further treatment with MeONa affords the desired compound (**15**).

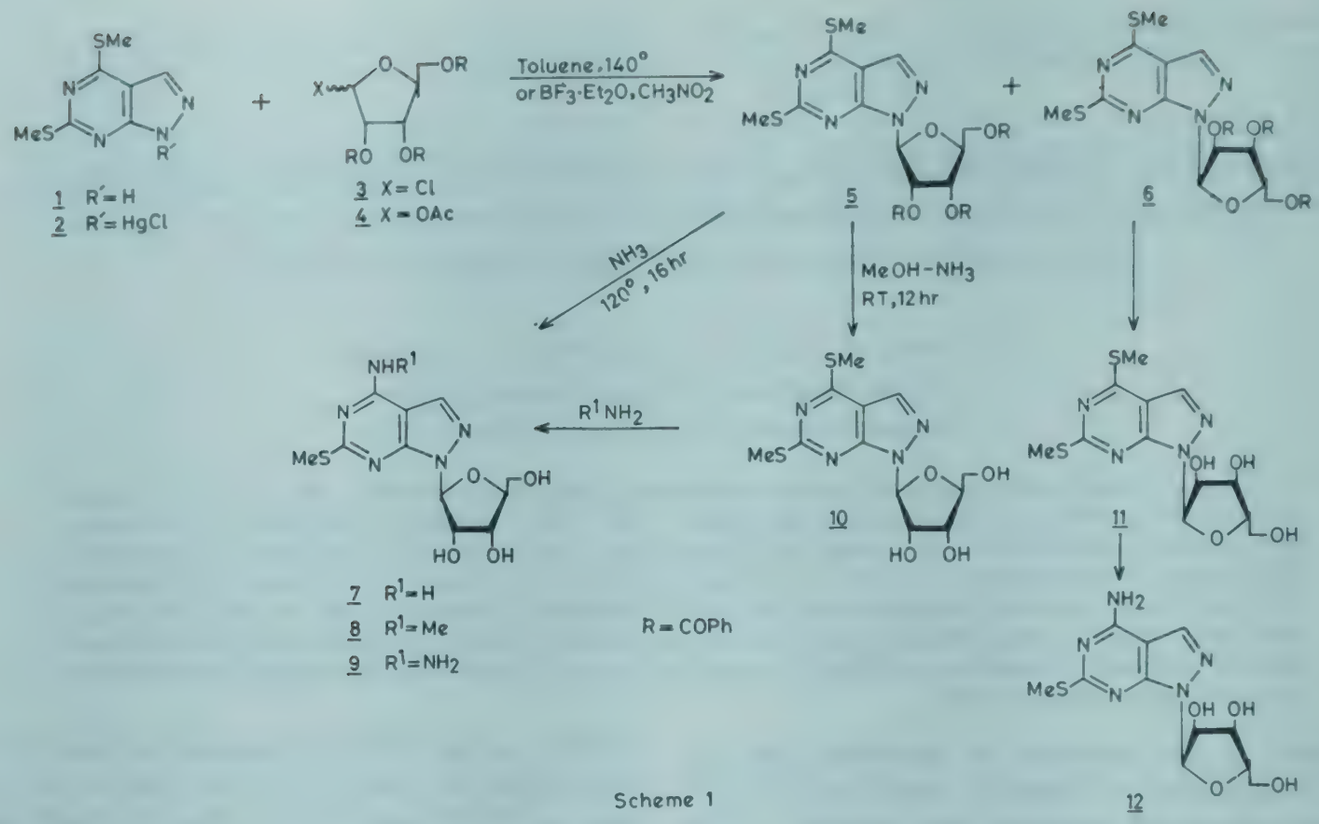
Interest in the synthesis of substituted pyrazolo[3,4-*d*]pyrimidine ribosides[1] was stimulated due to several reports suggesting that 4-amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (4-APP riboside) may act as a substrate for anabolic (adenosine kinase[2,3] and adenylate kinase[3,4]) and catabolic (adenosine deaminase) enzymes[3,5,6]. Experimental observations further indicated that as compared to 4-APP, 4-APP riboside is more effective inhibitor of both cell growth and *de novo* biosynthesis of purine. It was also observed that 4-APP riboside was an excellent substrate for adenosine kinase[2,3], whereas 4-APP was a poor substrate for adenine phosphoribosyl transferase. Prompted by these reports, it was thought worthwhile to synthesise some substituted pyrazolo[3,4-*d*]pyrimidine riboside as analogues of spongosine[7], a marine nucleoside[8]. In the present paper we report the synthesis of 4-aminosubstituted-6-methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidines (**8** and **9**), 4-amino-6-methylthio-1-(α-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**12**) and 4-amino-6-methoxy-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**15**).

4,6-Dimethylthiopyrazolo[3,4-*d*]pyrimidine (**1**)[9], the key intermediate, on treatment with $HgCl_2$ in the presence of sodium hydroxide gave the chloromercuri complex (**2**) in nearly quantitative yield. Condensation of **2** with 1-chloro-2,3,5-tri-O-benzoylribofuranose (**3**) yielded the protected β-riboside (**5**) as the major (60%) and the protected α-isomer (**6**) as the minor (5%) products (see Scheme 1). $BF_3 \cdot Et_2O$ catalysed condensation of **1** with ribofuranose (**4**) in nitromethane also yielded **5** (60%) and **6** (10%). To improve the yield of **5**, the reaction was also carried out in other solvents such as CH_3CN and CH_2Cl_2. However, there was no improvement in yield. Karbukh *et al.*[10] have reported the synthesis of **5** by fusion of **1** with tetra-O-acetyl-D-ribofuranose.

The mixture of α- and β-isomers was resolved on silica gel column. The UV data of **5** (λ_{max} 365, 230 nm) and **6** (λ_{max} 363, 230 nm) suggested that the ribose moiety is attached at position-1 of the heterocyclic moiety[11]. Further α- and β-configurations of the deblocked nucleosides (**11** and **10**) from **6** and **5**, respectively were discernible from their PMR data. Generally the signal for anomeric proton for β-isomer appears relatively at higher field than that of α-isomer and further the coupling constant of the anomeric proton in β-isomer is smaller as compared to that in α-isomer[12]. The signals for anomeric protons in **11** and **10** were at δ 6.25 ($J_{1',2'}=4$ Hz) and 5.89 ($J_{1',2'}=2.5$ Hz) and thus these nucleosides have α- and β-configurations respectively.

Deblocking of **5** with methanolic ammonia at ambient temperature gave 4,6-dimethylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**10**) in 70% yield. Amination of **10** with NH_3 at 120° in a steel bomb led to 4-amino-6-methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**7**) in 90% yield. Direct amination of **5** with NH_3 also resulted in **7**; however, better yield was obtained when the reaction was carried out in two steps. Amination of **10** with methylamine and hydrazine hydrate furnished **8** and **9** in 68 and 19% yields respectively (Scheme 1). Treatment of **5** with hydrazine hydrate, however gave **9** in 70% yield.

†CDRI Communication No. 3963.



Scheme 1

Deblocking of the protected **6** led to 4,6-dimethylthio-1-(α-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**11**). Amination of **11** resulted in 4-amino-6-methylthio-1-(α-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**12**) in reasonable yield (70%) (Scheme 1).

Acetylation of **7** (Py/Ac_2O) gave the tetraacetyl derivative (**13**) in 80% yield. $KMnO_4$ oxidation of **13** in acetic acid afforded the sulphone (**14**) (75%) (Scheme 2). Compound **14** when heated with sodium methoxide finally gave 4-amino-6-methoxy-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]-pyrimidine (**15**) in 70% yield. Alternatively oxidation of **5** with H_2O_2 in acetic acid gave the sulphone (**16**), which on treatment with sodium methoxide afforded **15**.

Experimental Procedure

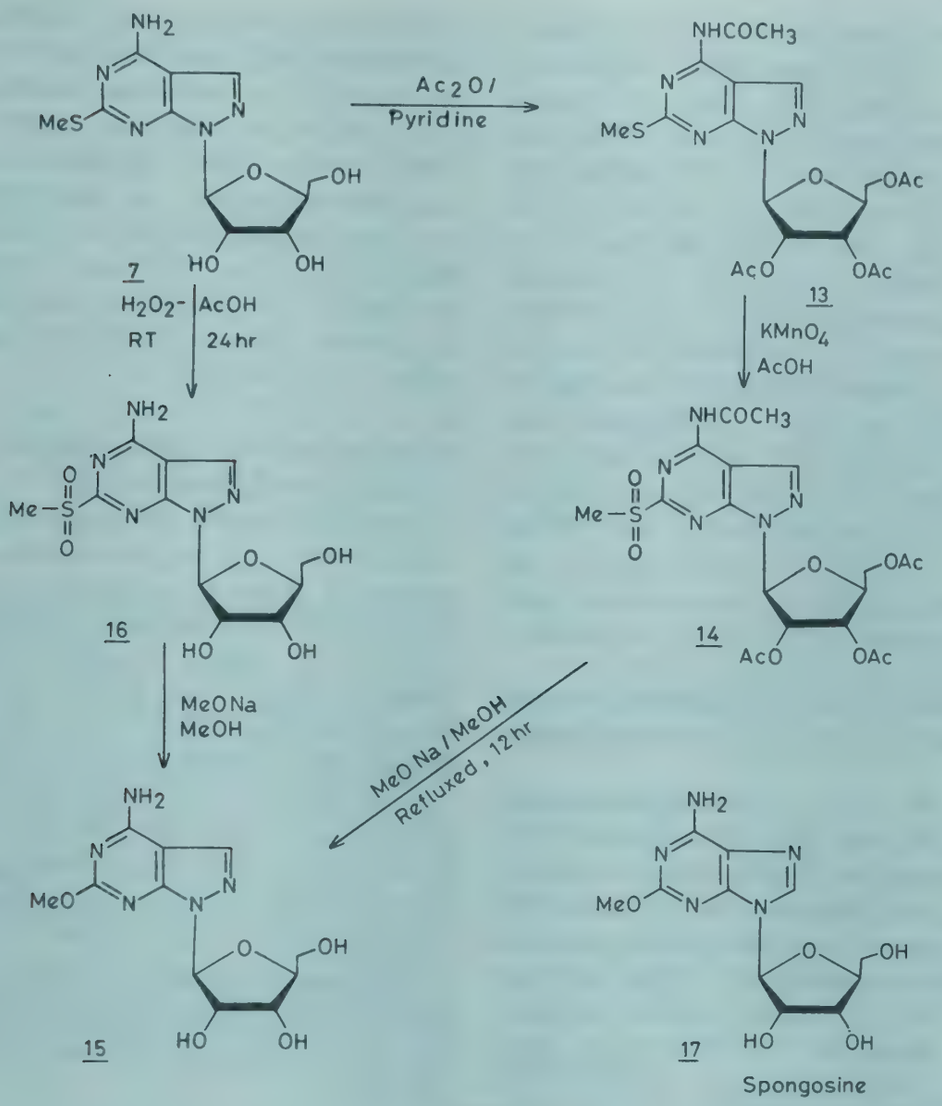
Melting points were taken with Büchi capillary apparatus (silicone bath) and are uncorrected. UV spectra were recorded on a Perkin Elmer-202 spectrophotometer (λ_{max} in nm), IR spectra on a Perkin-Elmer 157 grating infracord (ν_{max} in cm^{-1}) and mass spectra on a JEOL JMS-D300 instrument. The compounds were routinely checked for purity on silica gel plates and spots were located under UV lamp/by iodine vapours/spraying with 10% sulphuric acid in ethanol followed by heating at 100°/spraying with a mixture of *p*-anisaldehyde (2%) and sulphuric acid (10%) in ethanol followed by heating at 100°. Evaporation of solutions was carried out < 40°C under reduced pressure.

Ribosylation of 4,6-*dimethylthiopyrazolo*[3,4-*d*]-*pyrimidine* (**1**): (*a*) *Chloromercuri complex method*

To an azeotropically dried suspension of chloromercuri complex (**2**) (5 g, 11 mmol) of **1**[9] in anhyd. toluene (100 ml) was added slowly a solution of **3** (9 g, 18.7 mmol) in anhyd. toluene (50 ml) at 60°. After the addition was over the temperature of the reaction mixture was raised to 140° and refluxing continued for 4 hr. The resulting mixture was filtered while hot and the filtrate concentrated *in vacuo* to give a gummy mass which was extracted with $CHCl_3$ (300 ml). The organic extract was washed with KI (30%, 2 × 100 ml), water and dried (Na_2SO_4). Evaporation of the solvent gave a mixture (5.8 g) of ribosides (**5** + **6**).

4,6-*Dimethylthio*-1-(2′,3′,5′-*tri*-*O*-*benzoyl*-α-D-*ribofuranosyl*)*pyrazolo*[3,4-*d*]*pyrimidine* (**6**)

The mixture of ribosides (5.8 g) was chromatographed on SiO_2 (250 g) column. Elution with $CHCl_3$:MeOH (99.5:0.5, v/v) gave **6**, as colourless foam; yield 0.37 g (5%), m.p. 82-85°, sinters and melts at 115°; R_f 0.66 (C_6H_6:EtOAc 80:20); UV(MeOH): 263, 230; IR(KBr): 1740 (C=O); MS: 657 ($M^+ + 1$); PMR($CDCl_3$): 8.10-7.70 (*m*, 7H, H-3 and Ar−*H*), 7.6-7.1 (*m*, 9H, Ar−*H*), 6.71 (*d*, 1H, H-1′, $J_{1',2'} = 2$ Hz), 6.35-6.20 (*m*, 3H, H-4′ & H-5′), 2.62, 2.55 (each *s*, 3H, S−C*H*$_3$) (Found: C, 60.6; H, 4.2; N, 8.6. $C_{33}H_{28}N_4O_7S_2$ requires C, 60.4; H, 4.3; N, 8.5%).



SCHEME 2

4,6-Dimethylthio-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)pyrazolo[3,4-d]pyrimidine (**5**)

Continued elution of the SiO_2 column with $CHCl_3$:MeOH (99:1, v/v) gve **5** as colourless foam; yield 4.4 g (60%), m.p. 85-86°, sinters and melts at 120°; R_f 0.62 (C_6H_6:EtOAc 80:20); UV(MeOH): 265, 230; IR(KBr): 1740 (C=O); MS: 657 ($M^+ + 1$); PMR($CDCl_3$): 8.10 (*s*, 1H, H-3), 8.05-7.70 (*m*, 6H, Ar−*H*), 7.52-7.15 (*m*, 9H, Ar−*H*), 6.70 (*d*, 1H, H-1′, $J_{1',2'} = 1.8$ Hz), 6.35-6.15 (*m*, 2H, H-2′ & H-3′), 4.82-4.38 (*m*, 3H, H-4′ & H-5′), 2.55 (*s*, 3H, S−CH_3) and 2.50 (*s*, 3H, S−CH_3) (Found: C, 60.4; H, 4.6; N, 8.4. $C_{33}H_{28}N_4O_7S_2$ requires C, 60.4; H, 4.3; N, 8.5%).

(b) Boron trifluoride etherate catalysed condensation of **1** *with ribofuranose* (**4**)

A mixture of **1**, (1.6 g, 7.8 mmol) and 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (**4**) (3.9 g, 7.8 mmol) and dry CH_3NO_2 (100 ml) was refluxed. To it was added freshly distilled $BF_3 \cdot Et_2O$ (2 ml, 7.7 mmol) and refluxing continued for 1 hr. The solvent from the resulting mixture was evaporated under reduced pressure, the residue taken in ethyl acetate (200 ml), washed with aq. $NaHCO_3$ (2 × 100 ml) and dried (Na_2SO_4). Removal of the solvent gave a mixture of ribosides which was chromatographed over a column of SiO_2 (150 g) as above. Elution of the column with $CHCl_3 \cdot$MeOH (99.5:0.5 v/v) gave the α-isomer (**6**); (10%) and β-isomer (**5**) (60%).

Condensation of **1** with **4** in CH_3CN gave **6** (12%) and **5** (58%) and in CH_2Cl_2 gave **6** (5%) and **5** (40%).

4,6-Dimethylthio-1-(β-D-ribofuranosyl)pyrazolo-[3,4-d]pyrimidine (**10**) *and the corresponding α-isomer* (**11**)

A mixture of **5** (4 g, 2 mmol) and methanolic ammonia (150 ml, MeOH saturated with NH_3 at 0°) was kept at ambient temperature for 12 hr. Methanol and excess of NH_3 were removed under reduced pressure and the product subjected to flash chromatography on SiO_2 (180 g) column.

Elution with $CHCl_3$:MeOH (94:6, v/v) afforded **10** (yield 1.25 g, 60%), m.p. 185°; UV(MeOH): 278; IR(KBr): 3380 (OH); MS: 344 (M^+); PMR($CDCl_3$ + DMSO-d_6): 8.55 (*s*, 1H, H-3), 5.89 (*d*, 1H, H-1′, $J_{1',2'}$ = 2.5 Hz), 4.5-4.15 (*m*, 2H, H-2′ & H-3′), 4.30-3.88 (*m*, 2H, H-4′ & OH), 3.80-3.60 (*m*, 2H, H-5′), 2.60 (*s*, 3H, SCH_3), 2.50 (*s*, 3H, $S-CH_3$) (Found: C, 42.3; H, 4.7; N, 15.9. $C_{12}H_{16}N_4O_4S_2$ requires C, 41.9; H, 4.7; N, 16.3%).

Similar deblocking of **6** afforded **11** in 70% yield, m.p. 145°; UV(MeOH): 278, 258; IR(KBr): 3400 (OH), MS: 345 ($M^+ + 1$); PMR($CDCl_3$ + DMSO-d_6): 7.85 (*s*, 1H, H-3), 6.25 (*d*, 1H, H-1′, $J_{1',2'}$ = 4 Hz), 4.80-4.5 (*m*, 1H, H-2′), 4.48-4.35 (*m*, 1H, H-3′), 4.15-3.90 (*m*, 1H, H-4′), 3.75-3.50 (*m*, 2H, H-5′), 2.6 (*s*, 3H, $S-CH_3$), 2.52 (*s*, 3H, $S-CH_3$) (Found: C, 41.6; H, 4.8; N, 15.9. $C_{12}H_{16}N_4O_4S_2$ requires C, 41.9; H, 4.7; N, 16.3%).

4-Amino-6-methylthio-1-(β-D-ribofuranosyl)pyrazolo-[3,4-d]pyrimidine (**7**) *and the corresponding α-isomer* (**12**)

A mixture of **10** (1.5 g, 4.5 mmol) and methanolic-ammonia (30 ml MeOH, saturated with NH_3 at 0°) was heated at 120° in a steel bomb for 16 hr (14 hr for **11**). Methanol and excess of NH_3 were removed under reduced pressure and the product crystallised from EtOH to give the riboside[10] (7); yield 0.8 g (90%), m.p. 240°; UV(MeOH): 276, 242; IR(KBr): 3200-3500 (OH, NH_2); MS: 313 (M^+); PMR(DMSO-d_6): 8.80 (*s*, 1H, H-3), 7.50 (*bs*, 2H, NH_2), 6.10 (*d*, 1H, H-1′, $J_{1',2'}$ = 2.5 Hz), 4.5-4.2 (*m*, 2H, H-2′ & H-3′), 4.15-3.9 (*m*, 1H, H-4′), 3.85-3.55 (*m*, 2H, H-5′), 2.80 (*s*, 3H, $S-CH_3$) (Found: C, 42.5; H, 4.5; N, 22.8. $C_{11}H_{15}N_5O_4S$ requires C, 42.2; H, 4.8; N, 22.4%).

The compound **7** (yield 0.4 g, 60%) was also prepared directly from **5** (1.5 g, 4.5 mmol) by heating with methanolic-ammonia (40 ml) at 120° for 18 hr.

Similar ammination of **11** afforded **12** in 90% yield, which crystallised from aq. EtOH; m.p. 218°; MS: 313 (M^+); PMR(DMSO-d_6): 8.0 (*s*, 1H, H-3), 7.31 (*bs*, 2H, NH_2), 6.15 (*d*, 1H, H-1′, $J_{1',2'}$ = 4 Hz), 4.85-4.52 (*m*, 1H, H-2′), 4.41-4.20 (*m*, 1H, H-3′), 4.12-3.81 (*m*, 1H, H-4′), 3.70-3.50 (*m*, 1H, H-5′), 2.45 (*s*, 3H, $S-CH_3$) (Found: C, 42.3; H, 5.0; N, 22.0. $C_{11}H_{15}N_5O_4S$ requires C, 42.2; H, 4.8; N, 22.4%).

4-Methylamino-6-methylthio-1-(β-D-ribofuranosyl)-pyrazolo[3,4-d]pyrimidine (**8**)

A mixture of **10** (0.8 g, 2.3 mmol) and CH_3NH_2 (8 ml) was heated at 85° in a steel bomb for 2 hr. The excess of reagent was removed under reduced pressure and the crude product was chromatographed on SiO_2 (120 g) column. Elution with $CHCl_3$:MeOH (9:1, v/v) gave **8**, (yield 0.6 g, 68%) as colourless needles (EtOH), m.p. 132°; IR(KBr): 3400 (OH, NH); MS: 327 (M^+); PMR($CDCl_3$ + DMSO-d_6): 8.35 (*s*, 1H, H-3), 7.8 (*m*, 1H, N*H*), 5.72 (*d*, 1H, H-1′, $J_{1',2'}$ = 3 Hz), 4.55-4.1 (*m*, 2H, H-2′ & H-3′), 3.80-3.51 (*m*, 1H, H-4′), 3.5-3.1 (*m*, 2H, H-5′), 2.9 (*d*, 3H, NH-CH_3, *J* = 4 Hz), 2.61 (*s*, 3H, $S-CH_3$) (Found: C, 43.9; H, 5.4; N, 22.9. $C_{12}H_{17}N_5O_4S$ requires C, 44.0; H, 5.2; N, 22.4%).

4-Hydrazino-6-methylthio-1-(β-D-ribofuranosyl)-pyrazolo[3,4-d]pyrimidine (**9**)

A mixture of **10** (0.9 g, 2.6 mmol) and hydrazine hydrate (150 ml) was refluxed for 3 hr. The excess of reagent was removed under reduced pressure and the product chromatographed over SiO_2 (80 g) column. Elution with $CHCl_3$:MeOH (94:6,v/v) gave **9** (yield 0.17 g, 19%), colourless granule (EtOH), m.p. 143°; MS: 329 ($M^+ + 1$); PMR($CDCl_3$ + DMSO-d_6): 8.50 (*s*, 1H, H-3), 5.82 (*d*, 1H, H-1′, $J_{1',2'}$ = 3.5 Hz), 4.4-4.2 (*m*, 2H, H-2′ & H-3′), 4.15-3.90 (*m*, 1H, H-4′), 3.7-3.5 (*m*, 2H, H-5′), 2.4 (*s*, 3H, $S-CH_3$) (Found: C, 39.9; H, 5.0; N, 24.6. $C_{11}H_{16}N_6O_4S$ requires C, 40.2; H, 4.9; N,25.6%).

The compound **9** (yield 0.42 g, 70%) was obtained directly from **4** (1.2 g, 1.8 mmol) by heating at 120° for 12 hr with hydrazine hydrate (40 ml).

4-Acetamido-6-methylthio-1-(β-D-2′,3′,5′-tri-O-acetylribofuranosyl)pyrazolo[3,4-d]pyrimidine (**13**)

A mixture of **7** (1 g, 3.2 mmol), anhyd. pyridine (15 ml) and Ac_2O (2.5 ml) was stirred at ambient temperature for 2.5 hr. Water (3 ml) was added to the resulting mixture and excess of reagent and water removed under reduced pressure. The residue was chromatographed on a SiO_2 (80 g) column. Elution with $CHCl_3$:MeOH (98:2, v/v) gave **13** which crystallised from EtOH; yield 0.8 g (80%), m.p. 85-87°; IR(KBr): 1750 (C=O); PMR($CDCl_3$): 12.0 (*bs*, 1H, NH), 8.78 (*s*, 1H, H-3), 6.13 (*d*, 1H, H-1′, $J_{1',2'}$ = 2.5 Hz), 5.75-5.55 (*m*, 2H, H-2′ & H-3′), 4.45-4.00 (*m*, 3H, H-4′& H-5′), 2.49 (*s*, 3H, $S-CH_3$), 2.17, 2.02, 2.00, 1.96 (each *s*, 3H, $COCH_3$) (Found: C, 47.5; H, 4.9; N, 14.3. $C_{19}H_{23}N_5O_8S$ requires C, 47.4; H, 4.8; N, 14.6%).

4-Acetamido-6-methylsulphonyl-1-(β-D-2′,3′,5′-tri-O-acetylribofuranosyl)pyrazolo[3,4-d]pyrimidine (**14**)

A mixture of **13** (0.2 g, 0.4 mmol), AcOH (50%, 10 ml) and $KMnO_4$ (0.2 g) was stirred for

1 hr at 0°. Hydrogen peroxide (32%, 25 ml) was then added to it till the colour disappeared. The reaction mixture was extracted with chloroform, the organic extract washed with water, dried (Na_2SO_4), and the solvent removed under reduced pressure. The product, thus obtained, was crystallised from ethanol to give **14** as colourless needles, m.p. 114-16°; yield 0.18 g (75%); IR(KBr): 1140, 1320 (CH_3SO_2); PMR($CDCl_3$ + DMSO-d_6): 9.20 (*s*, 1H, H-3), 7.10 (*bs*, 1H, N*H*), 6.40 (*d*, 1H, H-1′, $J_{1',2'}$ = 1.8 Hz), 5.78-5.60 (*m*, 2H, H-2′ & H-3′), 4.50-4.15 (*m*, 3H, H-4′ & H-5′), 3.3 (*s*, 3H, SO_2CH_3), 2.25, 2.05, 2.02, 1.90 (each *s*, 3H, $COCH_3$) (Found: C, 44.6; H, 4.6; N, 14.0. $C_{19}H_{23}N_5O_{10}S$ requires C, 44.4; H, 4.5; N, 13.6%).

4-Amino-6-methoxy-1-(β-D-ribofuranosyl)pyrazolo[3,4-d]pyrimidine (**15**)

To a solution of **14** (0.3 g, 0.58 mmol) in absolute methanol (30 ml) was added MeONa (1 ml, 0.65 g Na in 12 ml absolute MeOH) and the mixture refluxed for 12 hr. The resulting mixture was cooled, neutralised with AcOH and evaporated under reduced pressure. The brown residue, thus obtained, was subjected to flash chromatography on SiO_2 (180 g) column. Elution with $CHCl_3$:MeOH (97:3, v/v) gave **15** (yield 0.14 g, 80%), colourless granule (H_2O), m.p. 240°; UV(MeOH); 285, 260; IR(KBr): 3200-3500 (NH_2, OH); MS: 297 (M^+), 298 ($M^+ + 1$); PMR($CDCl_3$ + DMSO-d_6): 8.45 (*s*, 1H, H-3), 7.45 (*bs*, 2H, NH_2), 5.75 (*d*, 1H, H-1′, $J_{1',2'}$ = 3.8 Hz), 4.58-4.32 (*m*, 2H, H-2′ & H-3′), 4.28-4.00 (*m*, 1H, H-4′), 3.75-3.65 (*m*, 2H, H-5′), 3.85 (*s*, 3H, OCH_3) (Found: C, 44.5; H, 5.2; N, 23.7. $C_{11}H_{15}N_5O_5$ requires C, 44.4; H, 5.0; N, 23.6%).

4-Amino-6-methylsulphonyl-1-(β-D-ribofuranosyl)-pyrazolo[3,4-d]pyrimidine (**16**)

To a solution of **7** (0.5 g) in glacial acetic acid (8 ml) protected from light was added H_2O_2 (30%, 1.8 ml). The mixture was kept at ambient temperature for 24 hr, ethanol (10 ml) added to it and evaporated. This process was repeated 4 times. The final residue, thus obtained, was crystallised from water to give **16** (yield 0.17 g, 32%), m.p. 259-60°; IR(KBr): 1120, 1365 (SO_2CH_3); PMR(DMSO-d_6): 8.01 (*s*, 1H, H-3), 7.82 (*bs*, 2H, NH_2), 6.15 (*d*, 1H, H-1′, $J_{1',2'}$ = 4 Hz), 5.22 (*m*, 2H, H-2′ & H-3′), 4.20 (*m*, 3H, H-5′ & H-4′), 3.55 (*s*, 3H, SO_2CH_3) (Found: C, 38.6; H, 4.8; N, 20.1. $C_{11}H_{15}N_5O_6S$ requires C, 38.3; H, 4.4; N, 20.3%). Compound **16** in absolute methanol was refluxed with MeONa for 8 hr to afford **15** in 70% yield.

Antiviral Assay

Ranikhet disease virus (RDV) was used for antiviral screening of the compounds. The strain of RDV, the haemagglutination test, the method of preparation of CAM culture, the optimal condition of infection by the virus are described in earlier publications[13,14]. The stationary culture of chriallantoic membrane of 10 to 12 days old chick embryos were prepared from white leg horn eggs.

Aqueous solution/suspension (0.1 mg/ml) of the compounds (**7** to **10**, **12**, **13**, **15** & **16**) were inoculated to each CAM culture using 6 CAM culture samples along with 0.064 HA/ml of RDV. The cultures were incubated at 37° for 48 hr. The percentage of inhibition of virus multiplication was assayed from the HA titre of the nutrient fluid of CAM culture infected with RDV.

The compounds (**10**) and (**15**) exhibited 40 and 50% inhibition respectively, **7** (20%) inhibition and **14** and **16** were found inactive.

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Synthesis & Antitubercular Activity of 4-(5-Nitro-2-furyl/2-pyrazinyl/1-adamantyl)-2-(alkyl/aryl/arylamino)thiazoles

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The reaction of haloketones, obtained from Arndt-Estert reaction on the acid chlorides of 1-adamantane, 5-nitrofuroic acid and pyrazine-2-carboxylic acid, with different thioamides and thioureas affords the title thiazoles (I-III). Some of them exhibit interesting antitubercular activity at 6.25 to 0.38 μg/ml concentration against $H_{37}Rv$ strain of *M. tuberculosis in vitro* testing. The structure activity relationship (SAR) has also been discussed.

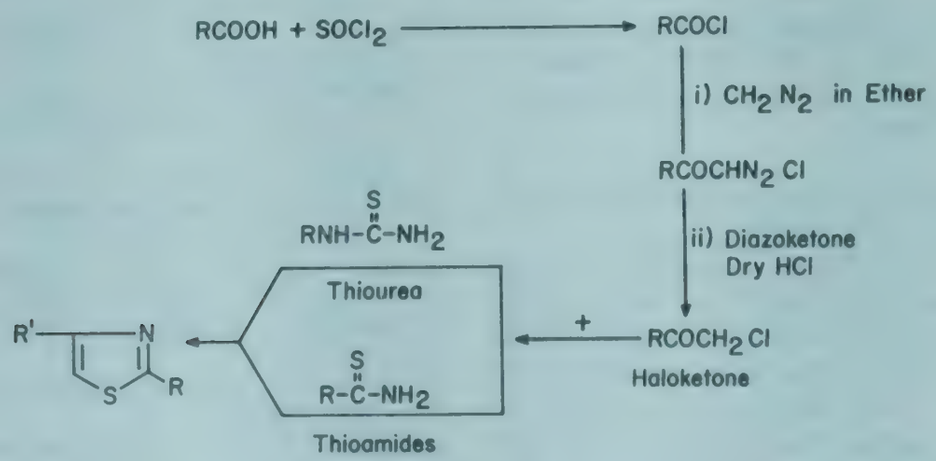
In view of good antibacterial[1] and antituberculosis[2] activities of thiazole derivatives bearing a nitrofuryl moiety, it was proposed to synthesize some new compounds of this type. The synthetic route was followed from 5-nitrofuroic acid which was converted into acid chloride by treatment with thionyl chloride. The acid chloride was subsequently treated with diazomethane (Arndt-Estert reaction) to get the corresponding diazoketone, which on decomposition with dry HCl gas afforded 5-nitro-2-furyl chloromethyl ketone. Similar procedure was followed to prepare 2-pyrazinyl chloromethyl and 1-adamantyl chloromethyl ketones starting from the corresponding acids. The haloketones, thus prepared, on reaction with alkyl/aryl thioureas and thioamides gave the title thiazoles (I-III) (Scheme 1). Their characterization data are given in Table 1.

Antituberculosis activities

The antituberculosis activity of the compounds was determined *in vitro* against the human virulent strain of *Mycobacterium tuberculosis* $H_{37}Rv$ following the method of Doub and Youmans[3] and the results are given in Table 1.

Incorporation of a pyrazine nucleus in thiazole moiety at 4-position did not generate any significant activity in the compounds as is evident from Table 1 (I_{1-25}). Compound I_{16} was, however, active at 12.5 μg/ml.

All the compounds of the series 2-substituted



I = R' = 2-Pyrazinyl
II = R' = 5'-Nitro-2'-furyl
III = R' = 1-Adamantyl
R = alkyl / aryl / arylamino

Scheme 1

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Table 1—Characterization Data of 4-(5'-Nitrofuryl/2-pyrazinyl/1-adamantylo-2-(alkyl/substituted-arylamino)thiazoles

Compd*	R	m.p. °C	Mol. formula†	Antituberculosis activity *in vitro* (μg/ml)‡
	R′ = 2-Pyrazinyl			
I_1	Benzyl	107-08	$C_{14}H_{11}N_3S$	50
I_2	*p*-Methoxyphenyl	119-20	$C_{14}H_{11}N_3OS$	—
I_3	3,4-Dimethoxyphenyl	146-47	$C_{15}H_{13}N_3O_2S$	—
I_4	3,4,5-Trimethoxyphenyl	151-52	$C_{16}H_{15}N_3O_3S$	—
I_5	3-Methoxy-4-propoxyphenyl	127-28	$C_{17}H_{17}N_3O_2S$	25
I_6	5-Chlorovanillino	238-39	$C_{14}H_{10}ClN_3O_2S$	—
I_7	5-Bromovanillino	247-48	$C_{14}H_{10}BrN_3O_2S$	—
I_8	3-Ethoxy-4-methoxyphenyl	151-52	$C_{16}H_{15}N_3O_2S$	—
I_9	*p*-Chlorophenoxyacetyl	148-49	$C_{14}H_{10}ClN_3OS$	—
I_{10}	2,3-Dichlorophenoxyacetyl	176-77	$C_{14}H_9Cl_2N_3OS$	—
I_{11}	2,4-Dichlorophenoxyacetyl	184-85	$C_{14}H_9Cl_2N_3OS$	200
I_{12}	Thymoxyacetyl	102-03	$C_{18}H_{20}N_3OS$	200
I_{13}	N,N-Dimethylaminophenyl	212-13	$C_{15}H_{14}N_4S$	—
I_{14}	*o*-Methoxyphenylamino	163-64	$C_{14}H_{12}N_4OS$	—
I_{15}	*m*-Methoxyphenylamino	178-79	$C_{14}H_{12}N_4OS$	—
I_{16}	*p*-Methoxyphenylamino	190-91	$C_{14}H_{12}N_4OS$	—
I_{17}	*o*-Ethoxyphenylamino	157-58	$C_{15}H_{14}N_4OS$	—
I_{18}	*p*-Ethoxyphenylamino	208-9	$C_{15}H_{14}N_4OS$	—
I_{19}	*p*-Chlorophenylamino	234-35	$C_{13}H_9ClN_4S$	—
I_{20}	2,4-Dichlorophenylamino	198-99	$C_{13}H_8Cl_2N_4S$	—
I_{21}	*p*-Tolylamino	207-08	$C_{14}H_{12}N_4S$	—
I_{22}	Benzylamino	192-93	$C_{14}H_{12}N_4S$	—
I_{23}	alpha-Phenylethylamino	128-29	$C_{15}H_{14}N_4S$	12.5
I_{24}	beta-Phenylethylamino	124-25	$C_{15}H_{14}N_4S$	1.56
I_{25}	2-Pyridylamino	278-79	$C_{12}H_9N_5S$	3.125
	R′ = 5-Nitro-2-furyl			
II_1	Methyl	143-44	$C_8H_6N_2O_3S$	0.78
II_2	Benzyl	130-31	$C_{14}H_{10}N_2O_3S$	0.39
II_3	*p*-Methoxyphenyl	227-28	$C_{14}H_{10}N_2O_4S$	6.24
II_4	3,4-Dimethoxyphenyl	165-66	$C_{15}H_{12}N_2O_5S$	0.39
II_5	3,4,5-Trimethoxyphenyl	172-73	$C_{16}H_{14}N_2O_6S$	0.39
II_6	3-Methoxy-4-propoxyphenyl	152-53	$C_{17}H_{16}N_2O_5S$	0.39
II_7	5-Chlorovanillino	209-10	$C_{14}H_9ClN_2O_5S$	0.78
II_8	5-Bromovanillino	218-19	$C_{14}H_9BrN_2O_5S$	0.78
II_9	3-Ethoxy-4-methoxyphenyl	172-73	$C_{16}H_{14}N_2O_5S$	1.56
II_{10}	*p*-Chlorophenoxyacetyl	181-82	$C_{14}H_9ClN_2O_4S$	1.56
II_{11}	2,3-Dichlorophenoxyacetyl	137-38	$C_{14}H_8Cl_2N_2O_4S$	0.39
II_{12}	2,4-Dichlorophenoxyacetyl	170-71	$C_{14}H_8Cl_2N_2O_4S$	1.56
II_{13}	Thymoxyacetyl	85-86	$C_{18}H_{19}N_2O_4S$	—
II_{14}	N,N-Dimethylaminophenyl	203-04	$C_{15}H_{13}N_3O_3S$	0.39
II_{15}	3-Pyridyl	173-74	$C_{12}H_7N_3O_3S$	0.78
II_{16}	4-Pyridyl	169-70	$C_{12}H_7N_3O_3S$	0.78
	R′ = 1-Adamantyl			
III_1	*p*-Methoxyphenyl	111-12	$C_{20}H_{23}NOS$	200
III_2	3,4-Dimethoxyphenyl	193-94	$C_{21}H_{25}NO_2S$	100
III_3	3,4,5-Trimethoxyphenyl	151-52	$C_{22}H_{27}NO_3S$	12.5
III_4	3-Methoxy-4-propoxyphenyl	114-15	$C_{23}H_{29}NO_2S$	6.25
III_5	5-Bromovanillino	205-06	$C_{20}H_{22}BrNO_2S$	50
III_6	*p*-Chlorophenoxyacetyl	96-97	$C_{20}H_{22}ClNOS$	—
III_7	2,4-Dichlorophenoxyacetyl	130-31	$C_{20}H_{21}Cl_2NOS$	1.56
III_8	3-Pyridyl	218-19 (d)	$C_{18}H_{20}N_2S$	6.25

(Contd)

Table 1—Characterization Data of 4-(5-Nitrofuryl/2-pyrazinyl/1-adamantylo-2-(alkyl/substituted-arylamino)thiazoles—(*Contd*)

Compd*	R	m.p. °C	Mol. formula†	Antituberculosis activity *in vitro* (μg/ml)‡
III_9	*m*-Methoxyphenylamino	153-54	$C_{20}H_{24}N_2OS$	3.125
III_{10}	*p*-Ethoxyphenylamino	161-62	$C_{21}H_{26}N_2OS$	200
III_{11}	*p*-Chlorophenylamino	185-86	$C_{19}H_{21}ClN_2S$	200
III_{12}	2,4-Dichlorophenylamino	171-72	$C_{19}H_{20}Cl_2N_2S$	—
III_{13}	β-Phenylethylamino	218-19 (d)	$C_{21}H_{26}N_2S$	6.25

*The yields of all the compounds were within the range of 55-68%.
†All the compounds gave satisfactory C, H and N analyses (within ± 0.4% of the theoretical values).
‡Standard drugs used were isoniazide (MIC = 0.04 μg/ml) and *p*-aminosalicylic acid (MIC = 0.4 μg/ml). (−) Indicates inactivity upto 200 μg/ml concentration.

4-(5′-nitro-2′-furyl)thiazoles showed activity at 0.39 to 6.25 μg/ml concentration. However, compound II_1 which bears an alkyl substituent, exhibited activity at 0.78 μg/ml. Similarly compound with benzyl substituent (II_2) and other substituted aromatic thiazoles (II_4, II_5, II_6, II_{11}, II_{14}) exhibited activity upto 0.39 μg/ml except *p*-methoxyphenyl thiazole which showed activity atg 6.25 μg/ml.

In the case of 2-substituted 4-(5′-nitro-2′-furyl)thiazoles it was specifically noted that the attachment of an aliphatic or a substituted aromatic nucleus to the thiazole moiety at its 2-position through a C-C bond imparts antituberculosis activity to the molecule.

However, in 2-substituted 4-(1′-adamantyl)thiazoles (Table 1; III_{1-8} and III_{9-13}) attachment of different groups (alkyl/heteroaryl/aryl) at 2-position of the thiazole nucleus either directly or through amino group did not produce any favourable effect.

Similarly, incorporation of an alicyclic moiety like adamantane into the thiazole nucleus (III_{1-13}) also did not impart significant antituberculosis activity to the compounds.

Thus, the antituberculosis activity of the title thiazoles is due to 5-nitro-2-furyl moiety rather than pyrazinyl or adamantyl moiety.

Experimental Procedure

Melting points were determined in H_2SO_4 bath and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer and PMR spectra in DMSO-d_6 or $CDCl_3$ on a Varian-100 spectrometer.

The required 5-nitrofuroic acid and pyrazine-2-carboxylic acid were prepared by literature methods.[4,5] Adamantane-1-carboxylic acid was procured from Fluka. Thioamides and thioureas were prepared by the literature method.[6,7]

2-(α-*Chloroacetyl*)*pyrazine*

To a dry ethereal solution of diazomethane (it is obtained from 10.3 g of nitrosomethyl urea and 15 ml aq. KOH solution, 50%) was added dropwise 2-pyrazinyl chloride (2.4 g, 0.016 mol) in dry benzene (50 ml), maintaining the reaction mixture below 5° under anhydrous condition. The reaction mixture was allowed to stand overnight at room temperature, and dry HCl gas bubbled through it in the cold till the evolution of nitrogen gas ceased. It was warmed to remove excess HCl gas, treated with charcoal, filtered and concentrated to get the title compound as yellow crystals, yield 2.3 g (87.45 %), m.p. 87.8° (Lit.[8], m.p. 89-89.5°).

1-(α-*Chloroacetyl*)*adamantane*

To a solution of diazomethane [obtained from nitrosomethyl urea (10.3 g) and potassium hydroxide (15.0 g; 50 %)] in dry ethanol was added dropwise adamantane-1-carbonyl chloride solution (7.5 g; 0.0025 mol) in dry benzene (100 ml) at a temperature below 0-5°. After keeping the reaction mixture overnight at room temperature, hydrogen chloride gas was passed until there was no evolution of nitrogen gas. The turbid solution was warmed to remove excess HCl gas, treated with charcoal, filtered and concentrated to get the crystals of the title compound, yield 6.5 g (80.96 %), identical (co-TLC) with an authentic sample.[9]

5-*Nitro*-2-*furoyl chloride*

To 5-nitro-2-furoic acid (15.0 g; 0.095 mol), were added freshly distilled thionyl chloride (10.0 ml) and dry benzene (50 ml). The reaction mixture was ref-

luxed for 2 hr in anhydrous condition, and excess thionyl chloride distilled off azeotropically with benzene to give the acid chloride as an oil, yield 12.0 g (72.0 %), m.p.38° (Lit.[10], m.p. 38-39°). It was used without further purification in the next step.

2-(α-*Chloroacetyl*)-5-*nitrofuran*

To a dry ethereal solution of diazomethane [obtained from nitrosomethyl urea (10.3 g) and potassium hydroxide (15.0 g; 50%)], was added 5-nitro-2-furoyl chloride (10.17 g; 0.057 mol) while maintaining the temperature below 5°. The reaction mixture was kept overnight at room temperature, filtered and HCl gas passed through it in the cold until evolution of nitrogen gas ceased. The excess HCl gas was removed by warming the mixture. Thereafter, it was treated with charcoal, filtered, concentrated and kept in a refrigerator to get the product as yellowish crystals, yield 6.25 g (57 %), m.p. 93° (Lit.[11], m.p. 92.5-94°).

3,4-*Dimethoxybenzonitrile* (*Veratronitrile*)

To a solution of veratraldehyde (8.3 g; 0.05 mol) in 95% warm ethanol (30 ml) was added a warm solution of hydroxylamine hydrochloride (4.2 g; 0.06 mol) in water (5 ml), on a water-bath. After stirring for 5 min, a solution of sodium hydroxide (3.0 g; 0.075 mol) in water (40 ml) was introduced into it through a dropping funnel. The mixture was stirred further for 10 min, kept at room temperature for 3 hr and crushed ice (25 g) added to it. It was saturated with carbon dioxide, kept in ice-chest for 2 days and the separated aldoxime filtered, washed thoroughly with cold water and air dried, yield 8.0 g (88.4%).

The above veratraldoxime (8.0 g; 0.04 mol) was heated on a burner with acetic anhydride (10.0 g; 94.96%) under anhydrous condition. The heating was discontinued after the boiling started. When the reaction subsided, heating was continued for half an hour. The reaction mixture was cooled to room temperature, poured on to crushed ice with stirring and the separated product filtered, washed with cold water and crystallized from ethanol to get veratronitrile, yield 6.0 g (78.5%), m.p. 65° (Lit.[12,13], m.p. 66.67°).

2-Ethoxy-4-methoxybenzaldehyde was prepared from ethyl vanillin yield 87%, m.p. 49.5° (Lit.[15], m.p. 50-51°).

p-Methoxybenzonitrile (*p*-anisonitrile); 3,4,5-trimethoxybenzonitrile; 3-methoxy-4-hydroxy-5-chlorobenzonitrile; 3-methoxy-4-hydroxy-5-bromobenzonitrile; 3-ethoxy-4-methoxybenzonitrile; 3-methoxy-4-propoxybenzonitrile; 4-N,N-dimethylaminobenzonitrile, etc. were prepared from the corresponding aldehydes following the procedure as described above for the preparation of veratronitrile from veratraldehyde.

3,4-*Dimethoxythiobenzamide*

Through a mixture of 3,4-dimethoxybenzonitrile (16.3 g; 0.1 mol), pyridine (25 ml) and triethylamine (6.0 ml) was passed dry hydrogen sulphide gas for 6 hr at room temperature. The reaction mixture was poured into cold water with stirring, filtered, washed with cold water and crystallised from ethanol to get the product as pale yellow needles; yield 14.78 g (75 %), m.p. 181-82° (Lit.[15], m.p. 184°).

2-*Benzyl*-4-(2′-*pyrazinyl*)*thiazole* (I_1; *Table* 1)

To a solution of thiobenzamide (0.302 g; 0.002 mol) in ethanol (25 ml) prepared by warming the mixture, was added 2-(α-chloroacetyl)pyrazine (0.313 g; 0.002 mol), and the reaction mixture refluxed for 2 hr, treated with charcoal, filtered and concentrated to get I_1, yield 0.375 g (75%); PMR ($CDCl_3$) : δ 9.3 (*s*, 1H, pyrazine C_1-H), 8.5 (*s*, 2H, pyrazine C_5 and C_6-H), 8.0 (*s*, 1H, thiazole proton), 7.3 (*s*, 5H, C_6H_5), 4.3 (*s*, 2H, C_6H_5-CH_2 –) (Found: C, 66.0; H, 4.5; N, 16.8. $C_{14}H_{11}N_3S$ requires C, 66.4; H, 4.4; N, 16.6%).

Other compounds of this series (I) were prepared in a similar manner by reacting the corresponding haloketones with appropriate thioamides or thioureas in ethanol.

2-*Methyl*-4-(5′-*nitro*-2′-*furyl*)*thiazole* (II_1, *Table* 1)

To a mixture of thioacetamide (0.15 g; 0.002 mol) and ethanol (25 ml) was added 2-(α-chloroacetyl)-5-nitrofuran (0.379 g; 0.002 mol) and the reaction mixture refluxed for 3 hr. The solid precipitated was dissolved in ethanol, treated with charcoal, filtered and concentrated to get II_1 as crystals, yield 0.269 g (62%) (Found: C, 45.3; H, 3.3; N, 13.3. $C_8H_6N_2O_3S$ requires C, 45.7; H, 2.9; N, 13.3%); PMR ($CDCl_3$): δ 7.7 (*s*, 1H, furan H-4), 7.4 (*d*, 1H, furan H-3), 7.00 (*d*, 1H, thiazole proton), 2.7 (*s*, 3H, CH_3).

2-(β-*Phenethylamino*)-4-(1′-*adamantyl*)*thiazole* (III_{13}; *Table* 1)

A mixture of β-phenylethylthiourea (0.360 g; 0.002 mol) and ethanol (25 ml) was warmed and 1-(α-chloroacetyl)-admantane (0.425 g; 0.002 mol) added to it. The reaction mixture was refluxed for 1 hr, treated with charcoal, filtered and concentrated to get III_{13}, yield 0.35 g (52%) (Found: C, 74.4; H, 7.7; N, 7.9. $C_{21}H_{26}N_2S$ requires C, 74.6; H, 7.7; N, 8.3 %); PMR ($CDCl_3$): δ 7.25 (*d*, 5H, C_6H_5), 6.3 (br, 1H, – NH), 6.0 (*s*, 1H, thiazole proton), 2.7-3.1 (*q*,

2H, C_6H_5-CH_2-CH_2-NH-), 3.3-3.9 (*m*, 2H, C_6H_5-CH_2-CH_2-NH-), 1.6-2.0 (*br d*, 15H, adamantyl protons).

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Notes

Synthesis of Oxygen & Sulphur Containing Crown Compounds under Solid-Liquid Phase Transfer Catalysis

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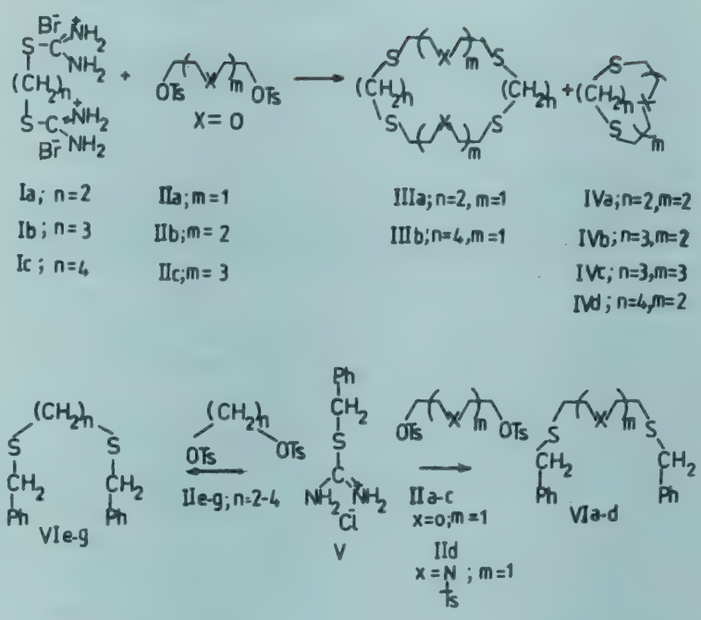
Sulphur containing crown compounds and podands have been synthesized by intermolecular nucleophilic displacements of tosylates with thiolate ions generated *in situ* under solid-liquid phase transfer catalysis.

Incorporation of sulphur in place of oxygen in macrocycles lowers their complexing ability towards alkali metals but favourably affects this character towards soft metals. This might, as a consequence, impart selectivity in macrocycle-induced transport of metal ions across organic membranes[1].

The synthesis of sulphur containing macrocycles has earlier been achieved by intermolecular reactions of appropriate thiols and halides[2,3]. Okahara's synthesis of macrocycles involving *in situ* formation of a tosylate and its intramolecular substitution by oxygen or nitrogen nucleophile constitutes a unique approach for oxygen and nitrogen containing macrocycles[4]. Similar substitution of a tosylate with thiolate ion which is a soft acid-base reaction has not been attempted probably because of the difficulty in the availability and ease of dimerization of thiols. Consequently, in the first instance, we have investigated the intermolecular reactions of ditosylates of glycols with thiolate ions generated *in situ* from thioiminium salts under solid-liquid phase transfer conditions[5].

Portionwise addition of the thiouronium salt (Ia)†, obtained from 1,2-dibromoethane and thiourea, to a stirred reaction mixture containing pulverised, fused potassium hydroxide, triethylbenzylammonium chloride (TEBA) and ditosylate of diethyleneglycol (IIa) in dry benzene furnishes 7, 16-dioxa-1, 4, 10, 13-tetrathiacyclooctadecane (IIIa) (2 : 2 stoichiometry) in 10% yield. Earlier IIIa was obtained[6] from dihalide of diethyleneglycol and ethane dithiol in 4% yield. Under non-PTC reflux conditions the product is formed in 5% yield. Similar reaction of Ia with ditosylate of triethyleneglycol (IIb) furnishes 1, 4-dioxa-7, 10-dithiacyclododecane (IVa) (1 : 1 stoichiometry) in 20% yield.



Thiouronium salt (Ib) of 1,3-dibromopropane and ditosylate (IIb) gives 8, 11-dioxa-1, 5-dithiacyclotridecane (IVb) (20%), while reaction of Ib with ditosylate of tetraethyleneglycol (IIc) furnishes 8, 11, 14-trioxa-1, 5-dithiacyclohexadecane (IVc) (10%).

The thiouronium salt (Ic) obtained from 1, 4-dibromobutane on reaction with ditosylate (IIa) gives 9, 20-dioxa-1, 6, 12, 17-tetrathiacyclodocosane (IIIb) (15%) and Ic with IIc gives 9, 12-dioxa-1, 6-dithiacyclotetradecane (IVc) (15%).

All the new compounds gave spectral data compatible with the structures assigned.

From these results it may be concluded that products with 1 : 1 stoichiometry are formed in cases where macro ring is 12 or more membered, otherwise 2 : 2 stoichiometry is preferred for the products.

Recent interest in podands[7]—open chain crown compounds—arises from both their complexing ability and ease in synthetic accessibility because fo the absence of often recalcitrant final cyclization step for macrocycles. Consequently, we have extended the above methodology involving use of thiolate ions generated *in situ* for the synthesis of sulphur containing podands. The reactions of benzylthiouronium salt (V) with ditosylates (IIa-g) have been performed under solid-liquid PTC by portionwise addition of V to the reaction mixtures containing pulverised fused potassium hydroxide, TEBA and IIa-g in dry benzene and the products (VI) are obtained in 30-55% yields. The reactions of V with IIa and IIb under non-PTC conditions give the products in 15-20% yields. These reactions when performed by stirring a reaction mixture containing all the reactants or on adding the dito-

†Amount of disulphide formed as a byproduct is controlled by the slow addition of the thiouronium salt.

sylate to a stirred reaction mixture of base, salt, catalyst and solvent give only dibenzyl disulphide as the major product. The use of this methodology in intramolecular cyclocondensation of thiolate and tosylate is being investigated.

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Preparation of Borondifluoro Chelates of Acridones

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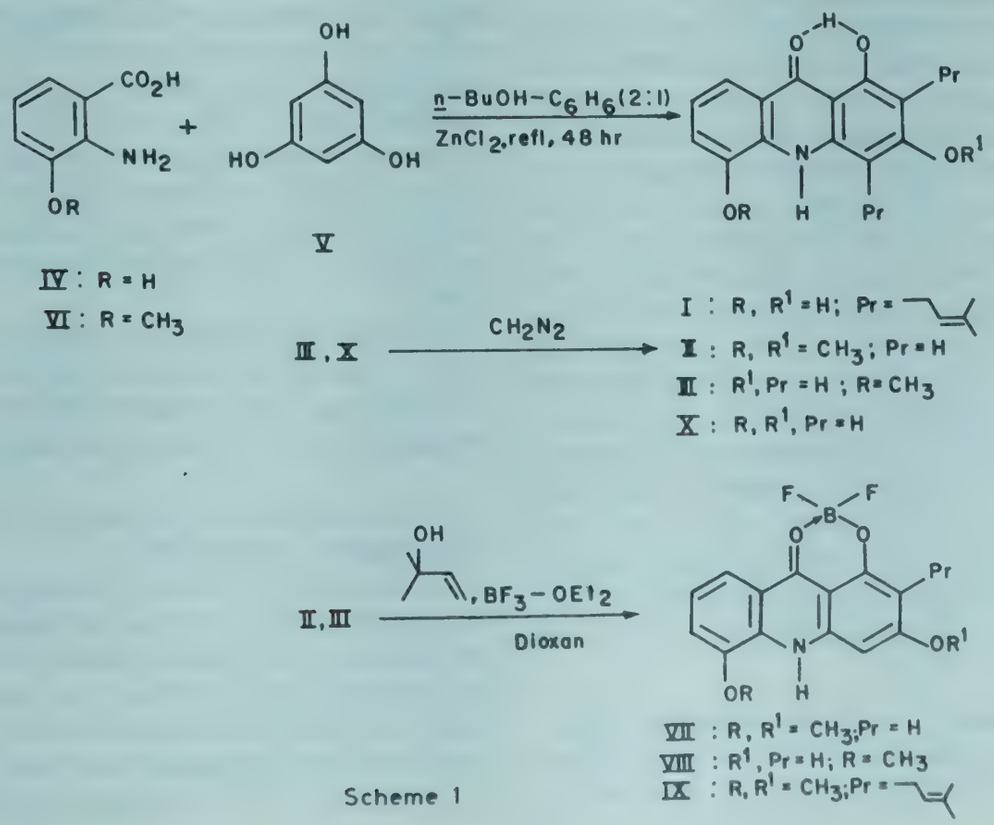
Isoprenylation of 1-hydroxy-3,5-dimethoxyacridone (II) and 1,3-dihydroxy-5-methoxyacridone (III) by 2-methyl-3-buten-2-ol in borontrifluoride-etherate at room temperature gives the highly stable and unusual borondifluoro chelates VII and VIII respectively. However, at an elevated temperature II yields the monoprenylated chelate (IX) in a good yield.

In our earlier attempt[1] towards the structural confirmation of the acridone based alkaloid atalaphylline (I) isolated[2] from *Atalantia monophylla* Correa (Rutaceae) both by degradative studies and total synthesis, we prenylated a number of hydroxyacridones. In this note, we wish to report the effect of substituents on the prenylation of acridones. For this purpose, we have prenylated 1-hydroxy-3,5-dimethoxyacridone (II) and 1,3-dihydroxy-5-methoxyacridone (III) under varying conditions.

The required acridones II[3] and III[4] were prepared by the reaction of phloroglucinol (V) with 3-hydroxyanthranilic acid (IV) and 3-methoxyanthranilic acid (VI) respectively at refluxing temperature of *n*-butanol and benzene containing anhyd. zinc chloride. To get II, the resultant product (X) was methylated with diazomethane (Scheme 1). The acridone II was treated[5] with 2-methyl-3-buten-2-ol in dioxan containing borontrifluoride-etherate to obtain a bright yellow solid (ethyl acetate), m.p. 304-7° (d), which did not respond to ferric chloride test for the presence of phenolic hydroxyl groups. It showed a strong fluorescence in solution. Its UV and IR spectra were identical with those of II except that the IR spectrum showed the absence of hydroxyl band and a down shift of carbonyl frequency. Its PMR spectrum exhibited no signals assignable to hydroxyl protons and isoprenyl moiety, but showed all other signals observed in the spectrum of II. Thus, the product was neither the expected prenylated derivative nor the reactant II as was evident from its MS (M^+ at m/z 319; M^+ of II at m/z 271), m.p. and TLC. The same yellow product, m.p. 304-7° (d) (ethyl acetate) was also obtained when borontrifluoride-etherate was added to a dioxan solution of II in the absence of a prenylating agent. This observation suggested that the yellow product was a boron and/or fluorine incorporated product of II.



Scheme 1

The M^+ peak of the solid was in agreement with the molecular formula $C_{15}H_{12}NO_4BF_2$. The absence of a hydroxyl group as shown by IR and PMR spectra and a down shift of νC = O suggested that the product was a borondifluoro chelate (VII) of II involving its carbonyl and hydroxyl groups.

A similar attempt was made with compound III to see the effect of methoxy and/or hydroxy groups. In this case also, a borondifluoro chelate (VIII) of III was obtained.

The failure of prenylation of the acridones II and III under the above condition was perhaps due to the low solubility of the chelates VII and VIII in the reaction mixture at room temperature. Moreover, O-prenylation occurs usually at carbons peri to hydroxyl groups[6]. Though, compound II contains a hydroxyl group at C-1, it is strongly bonded to C-9 carbonyl oxygen and could not take part in prenylation.

Prenylation of II and III was then tried under a more stronger condition. Thus, compound II on prenylation at refluxing temperature of solvents gave an orange solid (IX), m.p. 253-55° (ethyl acetate). However, under similar conditions, compound III yielded the chelate VIII. The IR of IX was similar to that of X. The PMR signals showed the presence of an isoprenyl moiety at C-2 (refs 4, 7-9). Hence, the compound was a borondifluoride chelate (X) of the prenylated acridone. Highly stable and unusual chelates such as VII, VIII and IX have also been reported earlier[10].

1-*Hydroxy*-3,5-*dimethoxyacridone* (*II*)[3]

A cold, ethereal solution of CH_2N_2 was added in excess to a cold solution of X (200 mg) in MeOH (50 ml), and the reaction mixture allowed to stand at room temperature overnight. After the removal of solvents, the product was chromatographed over alumina column to get II (120 mg), m.p. 215-18° (from pet. ether-EtOAc; 85:15); UV (EtOH): 204, 229, 256, 268, 277, 298, 312 and 388 nm (log ε 3.91, 3.44, 4.01, 3.79, 3.81, 3.46, 3.33 and 3.09); IR (nujol): 3370, 1665, 1610, 1575, 1250, 1165 and 800 cm^{-1}; PMR ($CDCl_3$): δ 8.56 (*s*, 1H, −N*H*− proton), 7.94 (*dd*, 1H, *J* = 7.5 and 2.5 Hz, C-8 proton), 7.14-7.30 (*m*, 2H, C-7 and C-6 protons), 6.30 (*s*, 1H, C-4 proton), 6.26 (*s*, 1H, C-2 proton), 4.09 (*s*, 3H, O*CH*$_3$) and 3.93 (*s*, 3H, O*CH*$_3$); MS (rel int): *m/z* 271 (M^+; 100%), 256 (28), 242 (7), 228 (3), 213 (5), 200 (4), 185 (8), 157 (2), 135 (9) (Found: C, 66.3; H, 4.7; M^+; 271. Calc. for $C_{15}H_{13}NO_4$: C, 66.4; H, 4.8%; Mol. wt 271.23).

1-*O-Borondifluoro*-3,5-*dimethoxyacridone* (*VII*)

(a): To a stirred solution of II (200 mg) in dioxan (50 ml) was added BF_3—OEt_2 (5 drops) followed by 2-methyl-3-buten-2-ol. The mixture was stirred for 24 hr at room temperature. The precipitate formed was filtered, washed with Et_2O and then with H_2O. The filtrate and the washings were diluted with water and extracted with EtOAc. The organic extract was dried and solvent removed under reduced pressure to give VII as a bright yellow solid (140 mg), m.p. 304-7° (d) (EtOAc).

(b): Borontrifluoride-etherate (2 drops) was added with stirring to a solution of II (40 mg) in dioxan (10 ml) and the mixture stirred at room temperature for 24 hr and extracted with Et_2O (5 × 100 ml). The ethereal extract was dried and concentrated to obtain VII as a bright yellow solid (20 mg), m.p. 304-7° (d) (EtOAc); UV (EtOH): 209, 214, 229, 256, 268, 278, 298, 312 and 289 nm (log ε 4.09, 4.08, 4.11, 4.60, 4.44, 4.48, 4.03, 4.91 and 3.65); IR (nujol): 1660, 1610, 1590, 1565, 1520 and 1075 cm^{-1}; PMR (DMSO-d_6): δ 7.90 (*q*, 1H, *J* = 2.5 Hz, C-8 proton), 7.26 (*m*, 2H, C-7 and C-6 protons), 7.18 (*d*, 1H, *J* = 2.0 Hz, C-4 proton), 6.46 (*d*, 1H, *J* = 2.0 Hz, C-2 proton), 4.16 (*s*, 3H, O*CH*$_3$) and 4.00 (*s*, 3H, O*CH*$_3$); MS (rel int): *m/z* 319 (M^+, 100%), 304 (91), 303 (91), 297 (35), 290 (17), 270 (19), 261 (16), 233 (23), 226 (9), 213 (14), 205 (13) (Found: C, 56.3; H, 3.7; M^+, 319. $C_{15}H_{12}NO_4BF_2$ requires C, 56.4; H, 3.8%; Mol. wt 319.10).

1-*O-Borondifluoro*-3-*hydroxy*-5-*methoxyacridone* (*VIII*)

(a): A mixture of III (500 mg), dioxan (100 ml), 2-methyl-3-buten-2-ol (0.5 ml) and BF_3-OEt_2 (10 drops) was stirred at room temperature for 24 hr and worked-up as usual to give VIII (270 mg) which recrystallized from EtOAc, m.p. 302-5° (d); UV (EtOH): 208, 225, 250, 267, 277, 282, 313, 328, 341 and 420 nm (log ε 4.23, 4.16, 4.34, 4.48, 4.48, 4.76, 3.81, 3.78, 3.73 and 3.59); IR (Nujol): 3550, 1655, 1613, 1570, 1540 and 1125 cm^{-1} (Found: C, 54.9; H, 3.1. $C_{14}H_{10}NO_4BF_2$ requires C, 55.2; H, 3.3%).

(b): The acridone III (40 mg) was treated with BF_3-OEt_2 (2 drops) as described above for compound VII. The usual work-up gave VIII (20 mg) which recrystallised from EtOAc, m.p. and m.m.p. 302-5° (d).

1-*O-Borondifluoro*-3,5-*dimethoxy*-2-(γ,γ-*dimethylallyl*) *acridone* (*IX*)

A mixture of II (100 mg), 2-methyl-3-buten-2-ol (0.5 ml), BF_3-OEt_2 (3 drops) and dioxan (40 ml) was refluxed for 16 hr, cooled, diluted with H_2O (50 ml) and extracted with EtOAc. The extract was dried (anhyd. Na_2SO_4) and solvent removed to give a solid which on chromatography over silica gel using pet. ether-EtOAc (75:25) as eluant furnished IX as a

crystalline compound (30 mg), m.p. 253-55° (EtOAc); UV (EtOH): 205, 221, 257, 289, 305, 315, 339 and 394 nm (log ε 4.55, 4.37, 4.62, 4.41, 4.15, 4.07, 3.59 and 3.74); IR (nujol): 3355, 1650, 1620, 1575, 1389, 1350, 1280, 1225, 1180, 1170, 1045 and 900 cm^{-1}; PMR (Me_2CO-d_6): δ 7.94 (*dd*, 1H, J=7.00 and 3.0 Hz, C-8 proton), 7.46-7.60 (*m*, 2H, C-7 and C-6 protons), 6.64 (*s*, 1H, C-4 proton), 5.20 (*m*, 1H, $-CH_2-CH=CMe_2$), 3.72 (*d*, 2H, J=7.0 Hz, $-CH_2-CH=CMe_2$) and 1.82 [*s*, 3H, $-CH_2-CH=C(CH_3)CH_3$], another methyl proton signal of *gem*-dimethyl group might have merged with the solvent acetone signal at 2.08; MS (rel int): *m/z* 387 (M^+, 48%), 372 (35), 339 (26), 332 (34), 320 (34), 310 (100), 318 (39), 284 (22), 271 (34) (Found: C, 61.8; H, 5.0; M^+ 387. $C_{20}H_{20}NO_4BF_2$ requires C, 60.0; H, 5.1%; Mol. wt 387.21).

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Aluminium Amalgam, a New Reagent in Glycal Synthesis†

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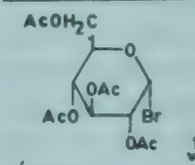
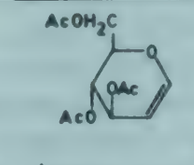
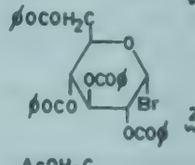
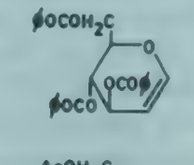
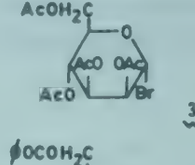
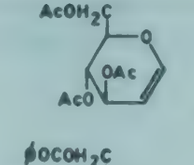
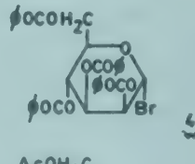
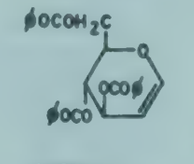
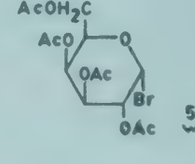
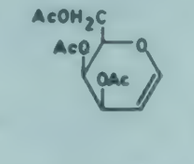
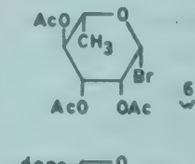
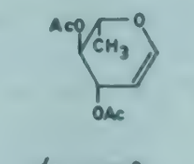
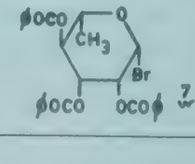
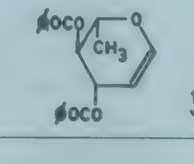
The glycals (**8-14**) have been synthesised by reduction of the corresponding glycosyl bromides (**1-7**) by aluminium amalgam. Glycals carrying acid-sensitive substituents can also be synthesised by the use of this reagent.

The glycals[1] are the key compounds in the synthesis of several groups of natural products[2-4], C-nucleosides[2], N-nucleosides[5], 2,3-unsaturated sugars[3,6] and have also been used in electrophilic addition reactions[7]. The glycal synthesis of Fischer and Zach[1] still remains the only general method although notable changes in the original method have been made by Helferich *et al*[8]. The key step in the modified method is the reduction of the bromide with zinc. Platinum[9] and copper[10] salts have also been used for catalysing the reduction step. However, this reductive method has its own limitations. It has been pointed out[9] that inadequate control of reaction temperature (0° to −15°) may result in the replacement of bromine by acetoxy group. Moreover, this method can not be extended for the reduction of acid-sensitive halo sugars. Glycals have also been produced in other reactions but these do not offer general preparative routes[11]. Aluminium amalgam is one of the mild reducing agents. In the present note, we report the synthesis of various pyranosyl glycals (**8-14**) by reduction of the corresponding bromo sugars (**1-7**) with aluminium amalgam.

Treatment of the D-glucose with brominating reagent (prepared from bromine, red phosphorous and gl acetic acid) afforded tetra-O-acetyl-α-D-glucopyranosyl bromide (**1**). Reduction of **1** with freshly prepared aluminium amalgam gave the glycal (**8**)[12] in good yield. This reaction was extended for the reduction of bromo sugars (**2-7**). The results are presented in Table 1.

The method has great potential as it can be employed for the synthesis of glycals carrying acid-sensitive substituents.

Table 1—Reaction Time and % Yield of Various Pyranosyl Glycals (**8-14**) in Aluminium Amalgam Reduction

Substrate	Product	Reaction time (hrs)	% yield
 **1**	 **8**	6	85
 **2**	 **9**	5	60
 **3**	 **10**	5	78
 **4**	 **11**	3	65
 **5**	 **12**	4	60
 **6**	 **13**	3	82
 **7**	 **14**	3	80

Tri-O-acetyl-D-glycal (**8**)

To the stirred brominating reagent (50 ml) [bromine (10 ml), red phosphorous (5 g) and gl AcOH (50 ml)] was added D-glucose (5 g) below 40°. The reaction mixture was stirred at ambient temperature for 6 hr, $CHCl_3$ (100 ml) added to it and poured into ice-H_2O (100 ml). The organic layer was separated and the aqueous layer extracted with $CHCl_3$ (3 × 100 ml); the combined $CHCl_3$ extract was washed with water, $NaHCO_3$, dried ($CaCl_2$) and evaporated under reduced pressure. The thick syrup thus obtained was crystallised with ether-pet. ether (40-60°) to furnish tetra-O-acetyl-α-D-glucopyranosyl bromide (**1**), m.p. 87-88° (lit.[8], m.p. 88-89°) identical with an authentic sample (m.m.p., IR, PMR, co-TLC).

To an ice-cooled stirred solution of **1** (7 g, 17 m mol) in aq. THF (2%, 420 ml) was added alumini-

†CDRI Communication No. 3960

um amalgam [freshly prepared by activating aluminium foil (4.6 g, 10 g atom) in 10% aq NaOH, washing with water, ethanol, ether, drying on a filter paper and then dipping in 2.5% aq $HgCl_2$ for a few seconds. It was again washed with dry ethanol and ether]. The reaction mixture was slowly warmed to room temperature and stirred for 6 hr and the solvent evaporated. To the residue, water was added and extracted with CH_2Cl_2 (4×100 ml). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude glycal, thus obtained, was subjected to flash chromatography over SiO_2 gel. Elution with hexane-ethyl acetate (93:7) furnished tri-O-acetyl-D-glycal (**8**) (yield 3.9 g, 85%), identical in all respects (IR, PMR, Mass) with an authentic sample.

The same procedure was applied for the preparation of other glycals (**9-14**).

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Synthesis of (9*Z*, 12*E*)-9,12-Tetradecadien-1-yl Acetate

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Synthesis of 1,4-dienyl acetate (**1**), a sex pheromone of many lepidopterous insects, has been accomplished. The approach involves carbon-carbon coupling via acetylene route, catalytic partial hydrogenation, reduction of propargylic alcohol to *trans* allylic alcohol and reductive elimination of mesylate (**8**).

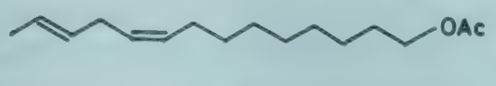
Several syntheses of the title compound (**1**), the sex pheromone component of many lepidopterous insects, especially the pests of stored grain and dried fruit have been reported[1-6]. In some of these, the important step involved allylation of acetylenes using either crotyl chloride or crotyl bromide. The two halo compounds often contain other isomers as impurities which are difficult to separate. In the synthetic strategy outlined in this note acetylenic route has been used employing easily accessible propargyl alcohol.

Propargyl alcohol was C-alkylated with 8-(2′-tetrahydropyranyloxy)octyl bromide[7] in liquid NH_3 using $LiNH_2$ as base to obtain **2**; yield 8 g (75%); b.p. 102°-5°/0.05 mm; IR (film): 3450, 2970, 2940, 1465, 1125, 1070, 910 cm^{-1}; PMR ($CDCl_3$): δ 1.3 (*m*, 12H, $6\times -CH_2-$), 1.7 (*m*, 6H, $3\times -CH_2-$), 2.0-2.4 (*m*, 2H, $-CH_2-C\equiv C-$), 2.9 (*bs*, 1H, D_2O exchangeable, OH), 3.2-4.0 (*m*, 4H, $2\times -OCH_2-$), 4.2 (*bs*, 2H, $-CH_2-OH$), 4.6 (*bs*, 1H, $-O\overset{|}{C}HO-$).

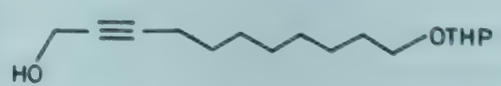
The alcohol (**2**) was subjected to partial hydrogenation using P-2 nickel catalyst[8], to afford *cis*-alcohol (**3**); yield 7.2 g (90%); b.p. 106-8°C/0.1 mm; IR (film): 3460, 2980, 2950, 1465, 1445, 1120, 1070, 1030, 910, 870, 820 cm^{-1}; PMR ($CDCl_3$): δ 1.3 (*m*, 12H, $6\times -CH_2-$), 1.7 (*m*, 6H, $3\times -CH_2-$), 1.9-2.3 (*m*, 2H, $-CH_2-CH=CH-$), 2.7 (*bs*, D_2O exchangeable, OH), 3.2-4.0 (*m*, 4H, $2\times -OCH_2-$), 4.2 (*d*, $J=5$ Hz, $-CH_2-OH$), 4.6 (*bs*, 1H, $O-\overset{|}{C}H-O$) 5.6 (*m*, 2H, $-CH=CH-$).

3 was mesylated and the mesylate (**4**) on reaction with NaI in acetone gave **5**; yield 7.2 g (76%); IR (film): 2975, 2950, 1470, 1460, 1345, 1125, 1080, 1030, 970, 910, 810, 815 cm^{-1}; PMR ($CDCl_3$): δ 1.3 (*m*, 12H, $6\times -CH_2-$), 1.7 (*m*, 6H, $3\times CH_2-$), 1.9-2.4 (*m*, 2H, $-CH_2-CH=CH-$), 3.1-4.2 (*m*, 6H, $2\times -CH_2O-$ and $-CH_2-I$), 4.65 (*br*, 1H, $-O-\overset{|}{C}H-O-$) 5.8 (*m*, 2H, $-CH=CH-$). Another molecule of propargyl alcohol was alkylated with **5** using ethylmagnesium bromide (2 equiv) as base, in the presence of anhydrous CuCl catalyst to yield 1,4-enyne alcohol (**6**); yield 3 g (66%); b.p. 130°-32°C/0.05 mm; IR (film): 3450, 2995, 2945, 1460, 1340, 1070, 1030, 980, 870, 815 cm^{-1}; PMR ($CDCl_3$): δ 1.3 (*m*, 12H, $6\times -CH_2-$), 1.7 (*m*, 6H, $3\times -CH_2-$) 1.9-2.3 (*m*, 3H, $-CH_2-CH=CH-$ & overlapped 1H, D_2O exchangeable $-OH$) 2.9 (*bm*, 2H, $-C\equiv C-CH_2-CH=CH-$), 3.2-4.0 (*m*, 4H, $2\times -OCH_2-$), 4.25 (*t*, 2H, $J=2$ Hz, $-CH_2OH$), 4.5 (*bs*, 1H, $-O-\overset{|}{C}H-O$), 5.3-5.9 (*m*, 2H, $-CH=CH-$].

Since **6** contains a propargylic alcohol unit, *trans* reduction of the triple bond was carried out by treating it with $LiAlH_4$, to obtain 1,4-diene al-



(**1**)



(**2**)

(**3**), R = OH
(**4**), R = OMs
(**5**), R = I
(**6**), R = $C\equiv CCH_2OH$

(**7**), R = OH
(**8**), R = OMs
(**9**), R = H

cohol (**7**); yield 2.5 g (80%); b.p. 128-30°C/0.03 mm; IR (film): 3450, 2990, 2945, 1465, 1350, 1125, 1070, 1030, 970, 810 cm^{-1}; PMR ($CDCl_3$): δ 1.3 (*m*, 12H, $6\times-CH_2-$), 1.7 (*m*, 6H, $3\times-CH_2-$), 1.9-2.2 (*m*, 2H, $-CH_2CH=CH-$), 2.0 (*bs*, 1H, D_2O exchangeable, OH) 2.8 (*bm*, 2H, $=HC-CH_2-CH$) 3.2-3.9 (*m*, 4H, $2\times-OCH_2-$), 4.1 (*d*, $J=4$ Hz, 2H, $-CH_2-OH$) 4.6 (*bs*, 1H, $-O-CHO-$), 5.4 (*m*, 2H, $-CH=CHCH_2-$), 5.7 (*m*, 2H, $-CH=CH-CH_2-OH$).

Mesylation of hydroxy group in **7** followed by reductive elimination of mesylate (**8**) with $LiAlH_4$ afforded C_{14}-tetrahydropyranyloxy compound (**9**). [IR (film): 2995, 2945, 1465, 1350, 1130, 1125, 1070, 1030, 970, 910, 820 cm^{-1}; PMR ($CDCl_3$): δ 1.3 (*m*, 12H, $6\times-CH_2-$), 1.7 (*m*, 9H, $3\times-CH_2-$, $CH_3-CH=CH$), 1.8-2.3 (*m*, 2H, $CH_2CH=CH-$). 2.7 (*bm*, 2H, $=CH-CH_2-CH=$), 3.2-4.1 (*m*, 4H, $2\times-CH_2-O-$), 4.6 (*bs*, 1H, $-O\overset{|}{C}HO-$), 5.4 (*m*, 4H, $2\times-CH=CH-$)]. Acetylation of **9** furnished the desired compound (1) [Yield 0.68 g (79%); b.p. 115-17°C/0.06 (lit[9] b.p. 110-12°C/0.04); IR (film): 3010, 2990, 2930, 1465,.1745, 1370, 1245, 1050, 965 cm^{-1}; PMR ($CDCl_3$): δ 1.3 (*m*, 10H, $5\times-CH_2-$), 1.55-1.80 (*m*, 5H, $-CH_2-CH_2OCOCH_3$ and $CH_3-CH=CH-$) 2.03 (*s*, 3H, $-O-COCH_3$, overlapped by a broad multiplet of 2H, $-CH_2CH=CH-$), 2.7 (*bm*, 2H, $=CH-CH_2-CH=$), 4.1 (*t*, $J=6$ Hz, 2H, $-CH_2-OCOCH_3$), 5.43 (*m*, 4H, $2\times-CH=CH-$) (Found: C, 76.3; H, 11.0. Calc. for $C_{16}H_{28}O_2$: C, 76.2; H, 11.1%].

The spectral data of our synthetic compound **1** are in agreement with those reported[10].

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Nitration of Olefinic & Acetylenic Fatty Acid Esters

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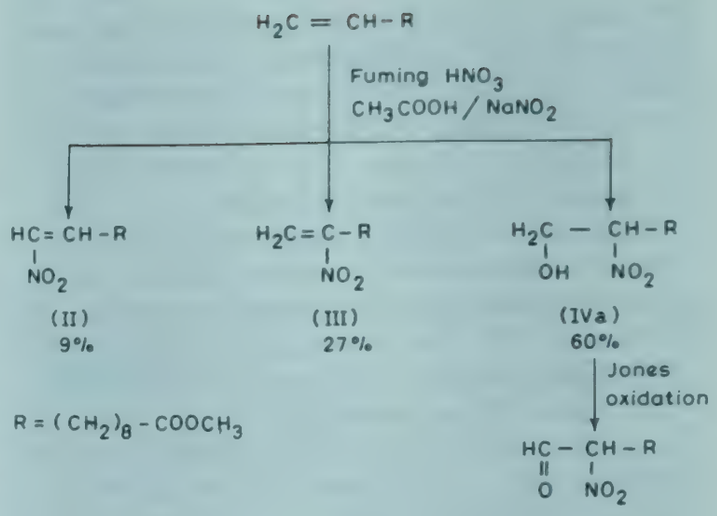
Methyl 10-undecenoate (I) on treatment with fuming nitric acid, sodium nitrite and gl. acetic acid produces two nitro-olefins in minor amounts characterized as methyl 11-nitro-10-undecenoate (II) and methyl 10-nitro-10-undecenoate (III) and a major product, methyl 11-hydroxy-10-nitroundecanoate (IV). Under similar conditions, methyl 10-undecynoate (Va) produces methyl 11-nitro-10-oxoundecanoate (VI) and methyl 9-undecynoate (Vb) furnishes methyl 11-nitro-10-oxoundecanoate (VII). However, methyl 9-octadecynoate (VIII) with excess HNO_3 affords methyl 9,10-dioxooctadecanoate (IX), half ester of azelaic acid (X) and methyl 11(10)-oxo-10(11)-nitrooctadecanoate (XI). Structures of these products have been established by their spectral data and elemental analyses.

Nitrogen derivatives of higher fatty acids are not found *per se* in natural fats. These compounds are useful as fibre lubricants, corrosion inhibitors, wax additives, plasticizers and pesticides. Conjugated nitroalkenes are very useful synthetic intermediates and although numerous procedures have appeared for the synthesis of such compounds[1,2], only a few methods have been described for introducing the nitro group into the fatty acid chain at the site of unsaturation[3,4]. As compared to olefinic unsaturation, the nitration of acetylenic unsaturation has received little attention[5]. We report herein the results of nitration of olefinic and acetylenic fatty acid esters.

Methyl 10-undecenoate (I) on nitration with fuming nitric acid in the presence of acetic acid and sodium nitrite at room temperature yielded three products (Scheme 1), separable by column chromatography. Compounds II and III showed characteristic IR bands at 1640 (C = C) and 1560, 1360 cm^{-1} (C–NO_2) indicating the presence of nitroolefinic group in the molecules. The PMR spectrum of II exhibited signals at δ 4.1 (*d*) and 6.8 (*m*) for C_{11}- and C_{10}-methine protons (O_2N-C*H*=CH- and O_2N-CH=C*H*-) respectively, suggesting its structure to be methyl 11-nitro-10-undecenoate. The mass spectrum further supported this structure ($M^{+\cdot}$ 243). From the PMR signal at δ 5.2 (CH_2=C-NO_2), we formulated compound III as methyl 10-nitro-10-undecenoate. Its MS gave additional support for this structure ($M^{+\cdot}$ 243). The major product (IVa) showed IR bands at 3400 (C-OH) and 1560, 1380



Scheme 1

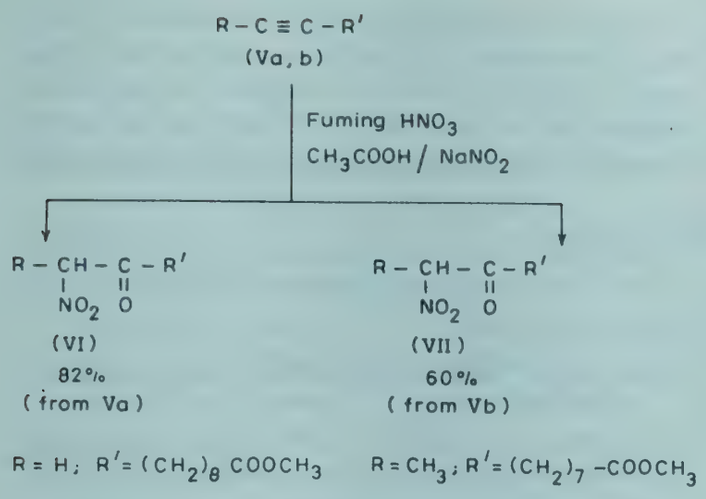
cm^{-1} (C-NO_2) which suggested it to be a nitrohydrin. The appearance of PMR signals at δ 3.6 (*m*) and 4.15 (*m*) for C_{11}-methylene and C_{10}-methine protons (OH-CH_2-C*H*-NO_2) supported its structure as methyl 10-nitro-11-hydroxyundecanoate (IVa). The structure was finally arrived at by MS which gave α-cleavage ions at *m/z* 230, 90 and 31.

The nitrohydrin (IVa), formed as a result of the addition of nitric acid, decomposes further to give the corresponding nitro-olefin (III). Isolation of the isomeric nitro-olefin II in small quantity supports the formation of the other isomer of IVa, i.e., methyl 10-hydroxy-11-nitroundecanoate, which might have escaped detection due to its small quantity.

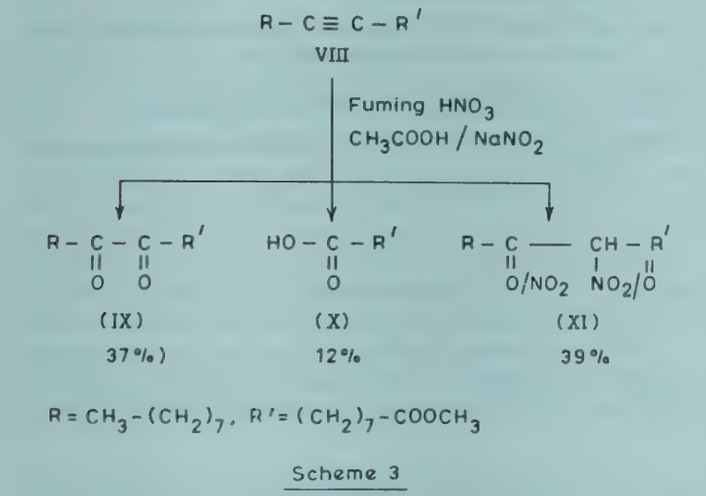
The nitrohydrin (IVa) on Jones' oxidation gave α-nitroaldehyde (IVb) which exhibited characteristic IR bands at 2810, 1710 (CHO) and 1560, 1340 cm^{-1} (C-NO_2).

Similar nitration of methyl 10-undecynoate (Va) showed the formation of a major and some minor products. The major product (VI; Scheme 2) was isolated in pure form and showed IR bands at 1730, 1705 and 1560, 1360 cm^{-1} due to keto and nitro functions respectively. From the PMR signal at δ 4.38 (CH_2NO_2-CO), its structure was deduced as methyl 11-nitro-10-oxoundecanoate (VI). Its MS showed fragment ions at *m/z* 199 and 60 besides $M^{+\cdot}$ at *m/z* 259, which further supported the proposed structure.

A similar nitration of methyl 9-undecynoate (Vb) gave VII as the only major product which was isolated and showed the presence of keto and nitro groups by IR bands at 1705 and 1550, 1370 cm^{-1} respectively. The PMR signals at δ 4.8 (*m*) and 1.5



Scheme 2



Scheme 3

(br *s*) for C_{10}-methine (CH_3-C*H*—NO_2) and C_{11}-methyl protons (CH_3-CH-NO_2) suggested its structure as methyl 10-nitro-9-oxoundecanoate. This structure was further supported by the mass fragmentation ions at *m/z* 244, 185, 102 and 74.

We were unable to detect the formation of the other isomer of VII, though its formation is expected on theoretical grounds. However, it is possible that this might have escaped detection along with other side products of the reaction.

Methyl 9-octadecynoate (VIII) on treatment with a slight excess of fuming nitric acid produced three products (Scheme 3). Product IX was found to be an α-diketo derivative. Product X was a cleavage product and characterized as the half ester of azelaic acid. On the basis of IR and PMR spectral data, product XI was suggested to be a keto-nitro derivative which was assumed to be an isomeric mixture of methyl 9(10)-nitro-10(9)-oxooctadecanoate. The $M^{+\cdot}$ peak at *m/z* 357 with other important fragmentation ions at *m/z* 216, 185, 141 and 59 in MS further supported the assigned structure XI. The formation of diketo and cleavage products in addition to keto-nitro derivative is attributed to the higher concentration of fuming nitric acid used in the reaction.

Analytical techniques were the same as described earlier[6]. 10-Undecynoic acid (R = H) and 9-octadecynoic acid (VIII) were synthesised by the method of Kannan *et al.*[7]. Synthesis of 9-undecynoic acid was carried out by the method of Ames and Bowman[8]. Elution of the column was usually effected with pet. ether containing increasing proportions of diethyl ether.

Olefinic esters I, Va,b (0.015 mol) and VIII (0.010 mol) were nitrated with fuming nitric acid (0.0176 and 0.238 mol respectively) in gl. acetic acid (25 ml). Simultaneously $NaNO_2$ was added to the reaction mixture in portions over a period of 1 hr. Thereafter, the reaction mixture was poured in cold water and extracted with ether, the ethereal extract washed slowly with sodium bicarbonate (10%) and water, dried (anhyd. Na_2SO_4) and solvent removed. The crude product thus obtained was purified by column chromatography using pet. ether-diethyl ether as eluent.

Ester I on nitration gave three products.

Product II (Found: C, 59.0; H, 8.7; N, 5.7%. $C_{12}H_{21}O_4N$ requires C, 59.2; H, 8.7; N, 5.8%); IR(neat): 1740, 1640, 1560, 1360 cm^{-1}; PMR(CCl_4): δ 6.8 (*m*, 1H), 4.1 (*d*, 1H), 3.5 (*s*, 3H), 2.2-2.4 (*m*, 4H), 1.25 (br *s*, 12H); MS: *m/z* 243 ($M^{+\cdot}$), 228, 211, 197, 184, 171, 157, 86, 72, 59.

Product III (Found: C, 59.0; H, 8.7; N, 5.7%. $C_{12}H_{21}O_4N$ requires C, 59.2; H, 8.7; N, 5.8%); IR(neat): 1740, 1640, 1560, 1360 cm^{-1}; PMR(CCl_4): δ 5.2 (*s*, 2H), 3.5 (*s*, 3H), 2.2 (*t*, 2H), 1.25 (br *s*, 14H); MS: *m/z* 243 ($M^{+\cdot}$), 211, 197, 184, 171, 157, 86, 72, 59.

Product IVa (m.p.53°) (Found: C, 55.1; H, 8.9; N, 5.4%. $C_{12}H_{23}O_5N$ requires C, 55.2; H, 8.9; N, 5.4%); IR(KBr): 3400, 1740, 1560, 1380 cm^{-1}; PMR(CCl_4): δ 4.15 (*m*, 1H), 3.6 (*m*, 2H), 3.5 (*s*, 3H), 2.65 (br *s*, 1H), 2.2 (*t*, 2H), 1.25 (br *s*, 14H); MS: *m/z* 261 ($M^{+\cdot}$), 244, 243, 230, 215, 202, 171, 140, 90, 72, 59. Jones' oxidation of IVa was conducted by the method adopted by Osman *et al.*[9] which produced IVb (m.p.65°); IR(CCL_4): 2810, 1710, 1560, 1340 cm^{-1}.

Va on nitration gave VI (Found: C, 55.6; H, 8.2; N, 5.4%. $C_{12}H_{21}O_5N$ requires C, 59.6; H, 8.2; N, 5.0%); IR(neat): 1740, 1705, 1560, 1360 cm^{-1}; PMR(CCl_4): δ 4.38 (*m*, 2H), 3.58 (*s*, 3H), 2.2-2.3 (*m*, 4H), 1.25 (br *s*, 12H); MS: *m/z* 259 ($M^{+\cdot}$), 244, 227, 213, 200, 199, 171, 157, 103, 102, 74, 60, 59.

Vb on nitration furnished VII (Found: C, 55.9; H, 8.2; N, 5.4. $C_{12}H_{21}O_5N$ requires C, 55.6; H, 8.1; N, 5.4%); IR(neat): 1740, 1710, 1550, 1370 cm^{-1}; PMR(CCl_4): δ 4.8 (*m*, 1H), 3.6 (*s*, 3H), 2.4 (*m*, 2H),

2.2 (*t*, 2H), 1.5 (br *s*, 3H), 1.25 (br *s*, 10H); MS: *m/z* 259 ($M^{+\cdot}$), 224, 227, 213, 200, 154, 117, 102, 74, 59.

Nitration of VIII gave the following products.

Product IX (m.p.54°) (Found: C, 69.9; H, 10.5. $C_{19}H_{34}O_4$ requires C, 69.9; H, 10.5%); IR(nujol): 1735, 1705 cm^{-1}; PMR(CCl_4): δ 3.6 (*s*, 3H), 2.6 (*t*, 4H), 2.2 (*t*, 2H), 1.25 (br *s*, 22H), 0.9 (*t*, 3H); MS: *m/z* 326 ($M^{+\cdot}$), 311, 294, 228, 217, 213, 185, 157, 141, 113, 59.

Product X(Found: C, 59.4; H, 8.9. $C_{10}H_{18}O_4$ requires C, 59.4; H, 9.0%); IR(nujol); 3400, 1740, 1715 cm^{-1}; PMR(CCl_4): δ 12 (br, *s*, 1H), 3.6 (*s*, 3H), 2.3 (*t*, 4H), 1.25 (br *s*, 10H); MS: *m/z* 203 (M + 1), 188, 185, 184, 171, 157, 74, 59.

Product XI (Found: C, 63.8; H, 9.9; N, 3.9. $C_{19}H_{35}O_5N$ requires C, 63.8; H, 9.9; N, 3.9%); IR(neat): 1740, 1715, 1550, 1370 cm^{-1}; PMR(CCl_4): δ 3.6 (*s*, 3H), 3.5 (*m*, 1H), 2.2-2.0 (*m*, 4H), 1.25 (br *s*, 24H), 0.9 (*t*, 3H); MS: *m/z* 357 ($M^{+\cdot}$), 342, 325, 311, 298, 216, 200, 172, 157, 141, 113, 59.

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Reaction of Hydroxylamine Hydrochloride with 2-Hydroxy-4′-methoxy-5-methyldibenzoylmethane & 4′-Methoxy-6-methylflavone

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2-Hydroxy-4′-methoxy-5-methyldibenzoylmethane (**1**) reacts with hydroxylamine hydrochloride in pyridine to give a mixture of 3-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)isoxazole (**2**) and 3-(α-hydroxyamino-4-methoxystyryl)-5-methylbenzisoxazole (**3**). Similar results are obtained from the reaction of **1** with hydroxylamine hydrochloride in ethylenediamine, aq. DMF, pyridine in ethanol or in the presence of KOH in methanol. However, in DMF or in the presence of sodium bicarbonate in ethanol only **2** is formed. Compound **1** remains unchanged in benzene/sodium bicarbonate and affords 4′-methoxy-6-methylflavone (**8**) in dil. acetic acid or methanol. Compound **8** reacts with hydroxylamine hydrochloride in pyridine or ethylenediamine to give 4′-methoxy-6-methylflavone oxime (**9**) instead of **2** as suggested by previous workers. 2-Hydroxy-5-methyldibenzoylmethane and 6-methylflavone also give similar results. The structures have been established by chemical studies and spectral data (UV, IR and PMR).

The reaction of dibenzoylmethanes with hydroxylamine hydrochloride has been shown to yield 3,5-diarylisoxazoles probably via oximes[1] in pyridine[2-4], ethylenediamine[5] or DMF[6] and isomeric isoxazoles in methanol[7] or in DMSO containing sodium acetate[8]. Similarly, flavones on reaction with hydroxylamine hydrochloride in pyridine[4,9] yield isoxazoles; however, Witczak *et al.*[10] have reported the formation of isomeric isoxazoles alongwith flavone oximes in such reactions. Further, while assigning the structures to different products, Basinski[11] suggested structures similar to **2** for the compounds responding to ferric chloride test while Kakade[8] suggested structures similar to **5** for the compounds responding to ferric chloride test. These contradictory results prompted us to reinvestigate this reaction under reported conditions.

2-Hydroxy-4′-methoxy-5-methyldibenzoylmethane (**1**) on refluxing with hydroxylamine hydrochloride in pyridine gave mixture of 3-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)isoxazole (**2**) and 3-(α-hydroxyamino-4-methoxystyryl)-5-methylbenzisoxazole (**3**). Compound **2** did not undergo deoximation and formed monoacetate (**4**), the IR spectrum of which showed no ν_{O-H} indicating the presence of only one OH group in **2**. All these observations and the spectra of **2** supported the suggested isoxazole structure. Moreover, the PMR spectrum of **2** indicated the phenolic proton to be hydrogen bonded with the nitrogen. This suggests that the nucleophile must have attacked the carbonyl carbon in **6** to form **2** instead of **5**. This product (**2**) was missed by earlier workers[2-4]. The product **3** also could not be deoximated but formed a monoacetate (**7**). Thus **3**, was identified as 3-(α-hydroxyamino-4-methoxystyryl)-5-methylbenzisoxazole instead of isoxazole as suggested by earlier workers[2-4].

Similar results were obtained from the reaction of **1** with hydroxylamine hydrochloride in different media such as ethylenediamine, aq. DMF, pyridine in ethanol and KOH in methanol. However, only **2** was obtained from the reaction performed in DMF or in the presence of sodium bicarbonate in ethanol. Compound **1** remained unchanged in the presence of sodium bicarbonate in benzene, but in acetic acid or in methanol it formed only 4′-methoxy-6-methylflavone (**8**) instead of the oximated product.

4′-Methoxy-6-methylflavone (**8**) remained unchanged with hydroxylamine hydrochloride in DMF, methanol or acetic acid, but formed 4′-methoxy-6-methylflavone oxime (**9**) in pyridine or in ethylenediamine. The product **9** underwent deoximation on refluxing with HCl/AcOH for 1 hr or with chromium trioxide in acetic acid, forming **8**. It formed a monoacetate **10**. All these observations and spectral data supported the structure **9** instead of **2** suggested earlier[4,9].

The reaction of 2-hydroxy-5-methyldibenzoylmethane and of 6-methylflavone with hydroxylamine hydrochloride also afforded similar products under identical conditions.

The formation of all these products can be explained by a mechanism suggested in Scheme 1. The NH_2OH adds on to enol **6** forming a hydroxyamino compound which undergoes cyclization involving either phenolic or enolic OH group forming the α-hydroxystyrylbenzisoxazole or isoxazole **2**. The former further reacts with hydroxylamine giving **3**. Thus, the products are formed by competitive reactions and the ratio of products is influenced by the

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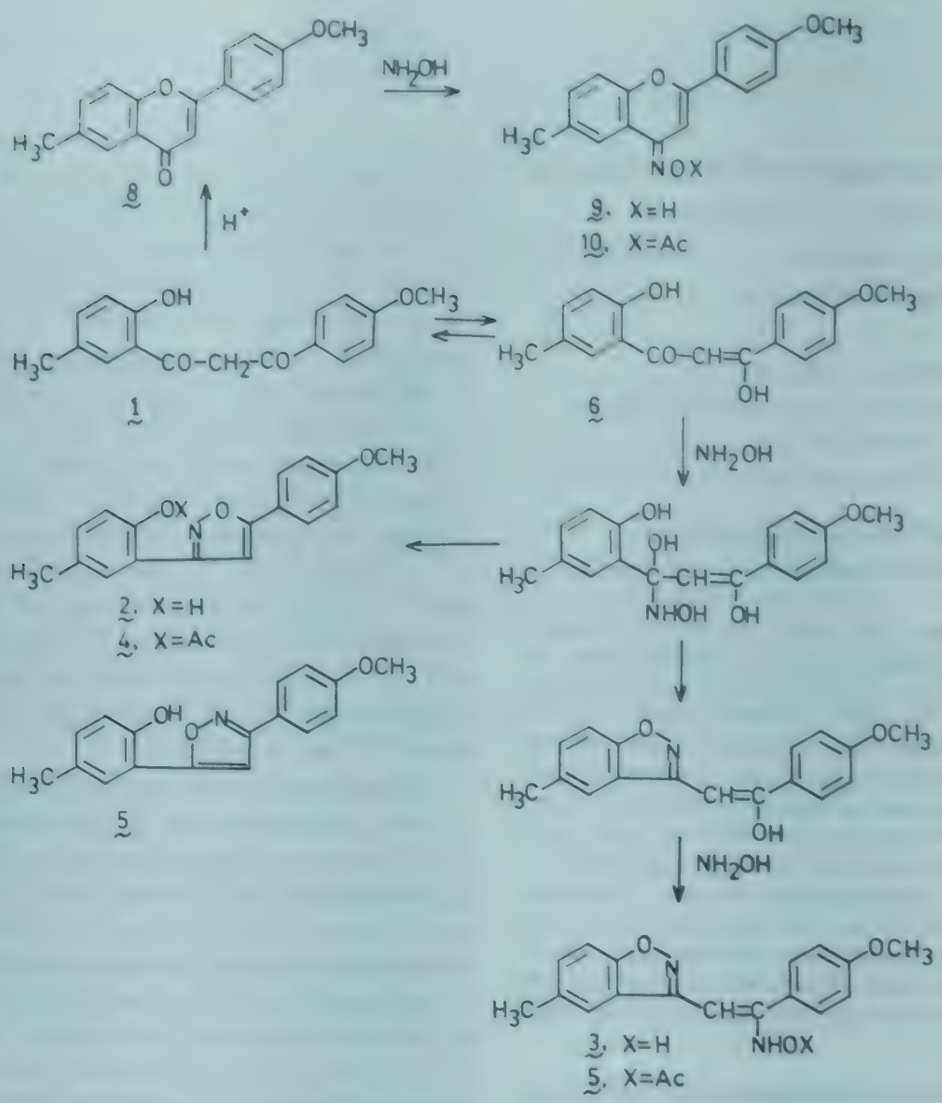

SCHEME 1

reaction medium or other conditions. In acidic medium the formation of flavone **8** instead of the oximated product is due to fast acid-catalysed cyclization of dibenzoylmethane. The formation of the flavone-oxime **9** from **8** is a simple oximation reaction.

Melting points were determined on a Neolab melting point apparatus using open capillaries and are uncorrected. PMR spectra were recorded on a Varian XL-100A high resolution NMR spectrometer using TMS as an internal standard (chemical shifts in δ, ppm), IR spectra on a Pye-Unicam SP2000 IR spectrophotometer in nujol (ν_{max} in cm^{-1}) and UV-VIS spectra in chloroform on an Aminco-Bowman DW 2A UV-VIS spectrophotometer (λ_{max} in nm). TLC was performed on silica gel-G layer (0.3 mm thick) using iodine vapours for visualization. Elemental analyses were carried out on a Coleman C, H analyser. The dibenzoylmethanes and flavones were prepared by known[5] methods.

Reaction of 2-hydroxy-4'-methoxy-5-methyldibenzoylmethane (**1**) *with hydroxylamine hydrochloride in pyridine*

To a solution of **1** (2.84 g, 10 mmol) in pyridine (20 ml) hydroxylamine hydrochloride (1.4 g, 20 mmol) was added and the mixture refluxed for 4 hr, cooled, diluted with water and acidified with 30% acetic acid to remove pyridine. The separated gummy mass was washed several times with water and triturated with ethanol to get a white product. It was boiled with carbon tetrachloride when the insoluble product 3-(α-hydroxyamino-4-methoxystyryl)-5-methylbenzisoxazole (**3**) separated out in pure form (1.4 g, 47%), m.p. 208°; R_f 0.40 (benzene) (Found: C, 70.5; H, 5.8. $C_{17}H_{16}O_3N_2$ requires C, 69.1; H, 5.4%); UV: 220, 269 and 313; IR: 3450 (O−H), 3100 (N−H), 1620 (C=N and C=C), 960 (=N−O), 800 (=CH wagging); PMR ($CDCl_3$): 1.56 (*s*, 1H, OH), 2.36 (*s*, 3H, Ar-CH_3), 3.90 (*s*, 3H, OCH_3), 6.46 (*s*, 1H, NH), 6.8-8.0 (*m*,

8H, Ar-*H* and =CH). Its ethanolic solution did not give any colour with neujtral ferric chloride. It remained unchanged in refluxing with AcOH for 3 hr or with HCl/AcOH for 30 min. On acetylation **3** gave 3-(αacetoxyamino-4-methoxystyryl)-5-methylbenzisoxazole (**7**), m.p. 120°; R_f 0.30 (benzene) (Found: C, 68.5; H, 5.9. $C_{21}H_{19}O_5N$ requires C, 69.1; H, 5.2%).

The carbon tetrachloride solution on concentration and cooling gave another white product, 3-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)isoxazole (**2**) (1.0 g, 36%), m.p. 150°; R_f 0.40 (benzene) (Found: C, 72.3; H, 6.4. $C_{17}H_{15}O_3N$ requires C, 72.6; H, 5.3%); UV: 254 and 292; IR: 3210 (intramolecularly H-bonded O−H), 1630-1620 (C=N and C=C), 950 (=N−O), 790 (=CH wagging); PMR ($CDCl_3$); 2.40 (*s*, 3H, Ar-C*H*$_3$), 3.94 (*s*, 3H, OCH_3), 6.83 (*s*, 1H, heteroaromatic H), 6.9-7.9 (*m*, 7H, Ar-*H*), 9.44 (*s*, 1H, OH). Its ethanolic solution gave a green colour with neutral ferric chloride. It remained unchanged on refluxing with AcOH for 3 hr or with HCl/AcOH for 1 hr and on acetylation gave 3-(2-acetoxy-5-methylphenyl)-5-(4-methoxyphenyl)isoxazole (**4**), m.p. 115°; R_f 0.38 (benzene) (Found: C, 70.3; H, 6.1. $C_{19}H_{17}O_4N$ requires C, 70.6; H, 5.3%); did not give ferric reaction.

The results of the same reaction carried out in other media are given in Table 1.

Reaction of 2-*hydroxy*-4′-*methoxy*-5-*methyldibenzoylmethane* (**1**) *with hydroxylamine hydrochloride in acetic acid or methanol*

To a solution of **1** (2.84 g) in acetic acid (20 ml) or methanol (50 ml) aq. solution of hydroxylamine hydrochloride (1.4 g in 5 ml) was added, the mixture refluxed for 4 hr, cooled, diluted with water, the separated product crystallised from ethanol and identified as 4′-methoxy-6-methylflavone (**8**) (2.6 g), m.p. 172°, on the basis of m.p., m.m.p., co-TLC and similar chemical and spectral properties.

Reaction of 4′-*methoxy*-6-*methylflavone* (**8**) *with hydroxylamine hydrochloride in pyridine or ethylenediamine*

Compound **8** (2.66 g, 10 mmol) and hydroxylamine hydrochloride (1.4 g, 20 mmol) were dissolved in pyridine (20 ml) or ethylenediamine (20 ml), and the solution was refluxed for 4 hr, cooled, diluted with water and acidified. The separated product was crystallised from ethanol to get 4′-methoxy-6-methylflavone oxime (**9**) (2.0 g and 1.9 g respectively), m.p. 237°. R_f 0.28 (benzene) (Found: C, 72.5; H, 5.8. $C_{17}H_{15}O_3N$ requires C, 72.6; H, 5.6%); UV: 253, 298 and 335; IR: 3200 (O−H), 1640 (C=N), 1090 (asymmetric νC−O−C), 815 (symmetric ηC−O−C), 960 (=N−O), 800 (=CH wagging); PMR ($CDCl_3$): 2.34 (*s*, 3H, Ar-C*H*$_3$), 3.84 (*s*, 3H, OCH_3), 6.9-8.0 (*m*, 8H, Ar-*H* and heteroaromatic H), 10.8 (*s*, 1H, OH). It underwent deoximation on refluxing with HCl/AcOH for 1 hr or on treatment with CrO_3/AcOH at 60-80° and on acetylation formed N-acetoxy-4′-methoxy-6-methylflavone oxime (**10**), m.p. 118°; R_f 0.13 (benzene) (Found: C, 70.1; H, 5.9. $C_{19}H_{17}O_4$ requires C, 70.6; H, 5.3%).

Table 1—Results of the Reaction of 2-Hydroxy-4-methoxy-5-methyldibenzoylmethane (**1**) with Hydroxylamine in Different Media

Sl No.	Reaction medium	Reaction period (hr)	Yield (%) of **2**	Yield (%) of **3**
1	Pyridine (20 ml)	4	35	47
2	Ethylenediamine (20 ml)	3	32	41
3	Dimethylformamide-water (30 ml, 5 ml)	2	43	41
4	Pyridine-ethanol (1.5 ml, 20 ml)	1	36	40
5	KOH-water-methanol (3.75 g, 10 ml, 50 ml)	3	35	30
6	Dimethylformamide (30 ml)	2	72	—
7	$NaHCO_3$-ethanol (1.7 g, 30 ml)	2	70	—

Similarly 2-hydroxy-5-methyldibenzoylmethane on treatment with hydroxylamine hydrochloride in different reaction media such as pyridine, ethylenediamine, aq. DMF, pyridine in ethanol or KOH in methanol, formed a mixture of 3-(2-hydroxy-5-methylphenyl)-5-phenylisoxazole (40, 36, 48, 32 and 32% respectively, m.p. 106°; acetate: m.p. 117°) and 3-(α-hydroxyaminostyryl)-5-methylbenzisoxazole (44, 36, 36, 48 and 44% respectively, m.p. 208°; acetate: m.p. 125°) but in DMF or in the presence of sodium bicarbonate in ethanol only the former was isolated (72 and 60%). In acetic acid or methanol it cyclised to 6-methylflavone which on treatment with hydroxylamine hydrochloride in pyridine or ethylenediamine afforded 6-methylflavone oxime (80 and 76%, m.p. 215°; acetate m.p. 112°).

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DDQ Oxidation of Flavan-4-ols — A New Method for Synthesis of Flavones

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Flavan-4-ols on oxidation with two mol of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene afford flavones as the major products and flavanones as the minor products.

Oxidation of flavan-4-ols with dimethyl sulfoxide in the presence of acetic anhydride[1-3] and sodium dichromate[4] was reported to produce flavanones only whereas it was reported[5] that 3-deoxyanthocyanidines were produced on oxidation of flavan-4-ols with benzoquinone and chloranil. DDQ has not been used in the oxidation of flavan-4-ols, though it has been shown[5] to oxidise flavan-3,4-diols to afford 3-hydroxyflavanones. In this note we report the results of oxidation of flavan-4-ols with DDQ.

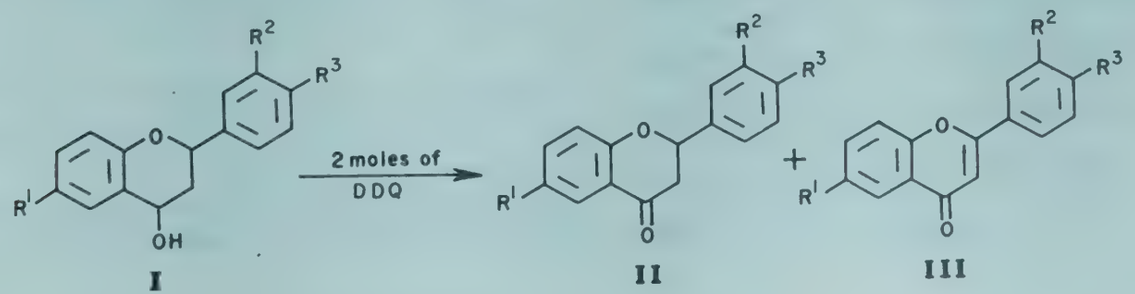
Oxidation of flavan-4-ol (Ia) by DDQ in refluxing benzene gave after work-up of the reaction mixture two products (TLC) which were separated by column chromatography. Both the products gave positive Shinoda test, indicating their flavonoid nature. IR spectrum of one of the products exhibited $\nu C=O$ at 1680 cm^{-1} while the UV spectrum in methanol displayed maxima at 250 (log ε 3.86) and 320 nm (log ε 3.3) characteristic of flavanones[6]. The identity of the product as the flavanone (IIa) was established by direct comparison (m.p., m.m.p. and IR) with an authentic sample.

Similarly oxidation of flavan-4-ols (Ib-f) with DDQ led to flavanones (IIb-f) as one of the products, the identities of which were established by direct comparison with authentic samples. The compounds are listed in Table 1.

The IR spectrum of the other product obtained exhibited $\nu C=O$ at 1640 cm^{-1}, characteristic of fla-

Table 1 — Pertinent Data on Compounds IIa-f and IIIa-f

Compd	m.p. °C (lit. m.p.)	Yield (%)
IIa	75 (75)[7]	16
IIb	97 (97)[8]	15
IIc	125 (126)[9]	18
IId	96 (97)[9]	15
IIe	106 (106-65)[10]	15
IIf	130 (130-1)[11]	15
IIIa	98 (98)[12]	70
IIIb	156 (157)[13]	68
IIIc	156 (156)[9]	75
IIId	182 (183-4)[10]	70
IIIe	180 (180-1)[10]	72
IIIf	194 (194-5)[14]	68



a) $R^1=R^2=R^3=H$

b) $R^1=R^2=H$; $R^3=OCH_3$

c) $R^1=H$; $R^2=R^3=OCH_3$

d) $R^1=Cl$; $R^2=R^3=H$

e) $R^1=Cl$; $R^2=H$; $R^3=OCH_3$

f) $R^1=Cl$; $R^2=R^3=OCH_3$

vones, while the UV spectrum displayed maxima at 250 (log ε 4.05) and 320 nm (log ε 4.20), also characteristic of flavones[6]. The flavone was identified as IIIa by direct comparison (m.p., m.m.p. and IR) with an authentic sample. Likewise other flavones (IIIb-f) were also fully characterised by direct comparison with authentic samples. The flavones (IIIa-f) are listed in Table 1.

Since flavanones are also formed in the reaction (15%) it is presumed that the first step in the reaction is the oxidation of alcohol to keto group. Second mol of DDQ is used in the dehydrogenation of flavanones to flavones. Oxidation of flavan-4-ols was also carried out with one mol of DDQ when both flavanones (20%) and flavones (30%) were formed, which confirms the above presumption.

Since the yields of flavones are good (~ 70%) this constitutes a facile method for the synthesis of flavones.

General procedure

A solution of flavan-4-ols (Ia-f) (1 mol) and DDQ (2 mol) in dry benzene was refluxed on a water-bath for 6-8 hr. 2,3-Dichloro-5,6-dicyano-1,4-hydroquinone that separated out was filtered off, the filtrate washed with aq sodium bisulfite, water, dried (Na_2SO_4) and the solvent removed under reduced pressure. The resulting solid was chromatographed over silica gel (200 mesh), to separate flavanones (IIa-f) and flavones (IIIa-f).

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Structural Confirmation of Thymusin

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The naturally occurring flavone, thymusin[5,6,4′-trihydroxy-7,8-dimethoxyflavone (I)] has been synthesised by SeO_2 cyclodehydrogenation of appropriately substituted chalcone, 4,5′-dibenzyloxy-2′-hydroxy-3′,4′,6′-trimethoxychalcone.

Ferreres *et al.*[1] isolated a new flavone, thymusin from *Thymus membranaceus* Linn and formulated it as 5,6,4′-trihydroxy-7,8-dimethoxyflavone (I) on the basis of spectral data alone. The present note describes the synthesis of I, thereby confirming the proposed structure (I) for thymusin.

The synthesis involves SeO_2 cyclodehydrogenation[2-7] of 4,5′-dibenzyloxy-2′-hydroxy-3′,4′,6′-trimethoxychalkone followed by treatment of the resulting flavone, 6,4′-dibenzyloxy-5,7,8-trimethoxyflavone with $AlCl_3$ in refluxing acetonitrile[8]. In the absence of an authentic sample of I, direct comparison of synthetic I could not be made. However, the spectral data of synthetic I tallied with those reported for thymusin[1].

Benzylation of 2,5-dihydroxy-3,4,6-trimethoxyacetophenone[9] with benzyl chloride gave 5-benzyloxy- 2-hydroxy-3, 4, 6 -trimethoxyacetophenone. This ketone (1 g) and *p*-benzyloxybenzaldehyde (1.5 g) in ethanol (20 ml) were treated with aq KOH (3 g in 30 ml), the reaction mixture kept at room temp for 48 hr, acidified with dil HCl and the chalkone thus obtained was crystallized from ethyl acetate-pet. ether as yellowish-orange needles (0.6 g), m.p. 163-65° (Found: C, 73.5; H, 5.9. $C_{32}H_{30}O_7$ requires C, 73.0; H, 5.7%).

The chalkone (1 g), SeO_2 (0.4 g) and freshly distilled isoamyl alcohol (15 ml) were refluxed for 72 hr in an oil-bath, selenium metal was filtered off and the filtrate concentrated to give 6,4′-dibenzyloxy-5,7,8-trimethoxyflavone which crystallised from ethyl acetate-pet. ether (0.7 g), m.p. 188-90° (Found: C, 74.0; H, 5.0. $C_{32}H_{28}O_7$ requires C, 73.2; H, 5.3%); PMR ($CDCl_3$): δ 3.77 (3H, *s*, $-OCH_3$), 3.84 (3H, *s*, $-OCH_3$), 3.85 (3H, *s*, $-OCH_3$), 5.0 (4H, *s*, $2\times -OCH_2C_6H_5$), 6.85 (1H, *s*, C_3-H), 7.30 (12H, *m*, $C_{3'}$-H, $C_{5'}$-H and $2\times -OCH_2C_6H_5$), 7.85 (2H, *d*, $J=9$ Hz, $C_{2'}$-H and $C_{6'}$-H).

The above flavone (0.3 g) in dry acetonitrile (5 ml) was treated with anhydrous $AlCl_3$ (400 mg) and the mixture refluxed for 4 hr. The acetonitrile was distilled off under reduced pressure, the residual mass acidified with HCl, and the solid obtained filtered and purified by fractional precipitation with ethyl acetate-pet. ether to give I (0.19 g), m.p. 230°; UV (MeOH): 308, 280 nm; +NaOMe: 402, 334, 280 nm; +$AlCl_3$: 436, 404, 306, 270 nm; +$AlCl_3$ +HCl: 434(sh), 364, 312, 282 nm; +NaOAc: 306, 348, 382 nm; +NaOAc +H_3BO_3: 306, 332, 392 nm; PMR ($CDCl_3$): δ 3.94 (3H, *s*, $-OCH_3$), 4.39 (3H, *s*, $-OCH_3$), 5.10 (1H, *s*, $-OH$), 6.53 (1H, *s*, C_3-H), 6.97 (2H, *d*, $J=9$ Hz, $C_{3'}$-H and $C_{5'}$-H), 7.34 (2H, *d*, $J=9$ Hz, $C_{2'}$-H and $C_{6'}$-H), 12.76 (2H, *s*, $2\times -OH$) (Found: C, 62.0; H, 4.4. $C_{17}H_{14}O_7$ requires C, 61.7; H, 4.2%).

My grateful thanks are due to Prof N R Bannerjee for guidance.

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Synthesis of 2,3-Dimethoxy-*p*-cymene

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A simple and straightforward synthesis of the title compound (**1**) is described starting from menthone (**2**). The synthetic 2,3-dimethoxy-*p*-cymene (**1**) is not identical with the natural product reported by Zutshi and Bokadia [*Indian J Chem*, **14B** (1976) 711].

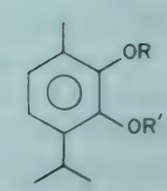
Although the natural occurrence of 2,5-dihydroxy-*p*-cymene and the corresponding mono and dimethyl ethers in several essential oils is well known[1-5], there is a solitary reference on the isolation of 2,3-dimethoxy-*p*-cymene (**1**) from the essential oil of *Laggera aurita*[6] (Schultz). Because of its rare occurrence it was thought desirable to confirm structure (**1**) by synthesis. We report herein the synthesis of title compound starting from menthone (**2**).

The diosphenol (**3**) obtained upon refluxing menthone (**2**) with hydrated ferric chloride in acetic acid was methylated to the corresponding methyl ether (**4**) with dimethyl sulphate in acetone under anhydrous conditions. Selenium dehydrogenation of (**4**) at 300°C for 2 hr afforded 2-methoxythymol (**5**) which without purification was subjected to methylation to yield **1**.

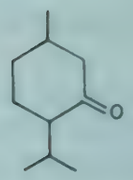
Compound (**1**) analysed for $C_{12}H_{18}O_2$ and displayed characteristic IR bands at 1570, 1600 and 810 cm^{-1} (1,2,3,4-tetrasubstituted aromatic ring); and 1020, 1270 cm^{-1} (aromatic-OCH_3). Its PMR spectrum in $CDCl_3$ exhibited signals at δ 1.12 [*d*, 6H, J=6.6 Hz, $-CH(CH_3)_2$], 2.09 (*s*, 3H, $Ar-CH_3$), 3.03 (*m*, 1H, $Ar-CH(CH_3)_2$, 3.57 and 3.6 (*s* each, 3H, $Ar-OCH_3$) and 6.45 (*s*, 2H, $Ar-H$). The PMR data broadly tallied with those reported for 2,3-dihydroxy-*p*-cymene[7], except for the signals at δ 3.57 and 3.60 for the two $-OCH_3$ groups instead of asinglet at δ 5.28 which was assigned to $-OH$ protons. The chemical shifts of synthetic 2,3-dimethoxy-*p*-cymene did not agree with those reported for the natural product[6] and hence assignment of 2,3-dimethoxy-*p*-cymene structure by Zutshi and Bokadia[6] calls for a fresh look.

Diosphenol (**3**)

Menthone (**2**) (10 g) was refluxed with hydrated $FeCl_3$ for 1.5 hr in 50% CH_3COOH (100 ml), extracted with ether, the ether extract washed with H_2O, aq $NaHCO_3$, water, dried and concentrated. On cooling it, crystals of **3** separated out which were washed with cold petroleum ether and finally purified by sublimation, m.p. 81-82°, yield 0.75 g; IR: ν 3460 ($-OH$), 1675, 1640 and 940 (enolized 1,2-diketone), 1390 and 1368 cm^{-1} [$-CH(CH_3)_2$].

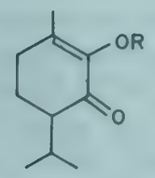


1, R = R' = OCH_3



2

5, R = CH_3, R' = H



3, R = H
4, R = CH_3

Diosphenol methyl ether (**4**)

A solution of **3** (0.75 g) in dry acetone (25 ml) containing anhydrous K_2CO_3 (4 g) and $(CH_3)_2SO_4$ was refluxed for 24 hr, filtered, the filtrate taken in ether, washed with H_2O, dried and concentrated. The crude product (**4**) was purified by using petroleum ether for chromatography, yield (0.516 g), b.p. 231°; IR: 1020, 1200 cm^{-1} ($-OCH_3$) and 1665 cm^{-1} (conjugated $>C=O$).

2,3-*Dimethoxy-p-cymene* (**1**)

Methyl ether (**4**, 2.3 g) was dehydrogenated with selenium (4 g) at 300°C for 2 hr. The reaction product was extracted with ether and concentrated. The crude product (1.896 g) containing the unreacted methyl ether was methylated with $(CH_3)_2SO_4$ under anhydrous conditions to yield crude **1** (0.108 g) which was purified by chromatography over silica gel and elution with petroleum ether; IR: 1570, 1600, 810, 1020 and 1270 cm^{-1}; PMR: δ 1.12 (*d*, 6H, J=6.6 Hz), 2.09 (*s*, 3H); 3.03 (*m*, 1H); 3.57 (*s*, 3H); 3.6 (*s*, 3H) and 6.45 (*s*, 2H).

We thank Dr Aravind Geda for the spectral data of natural compound.

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Synthesis of 3-Aryl-1H,3H-quinazolin-2,4-diones & Their 2-Thio Analogues

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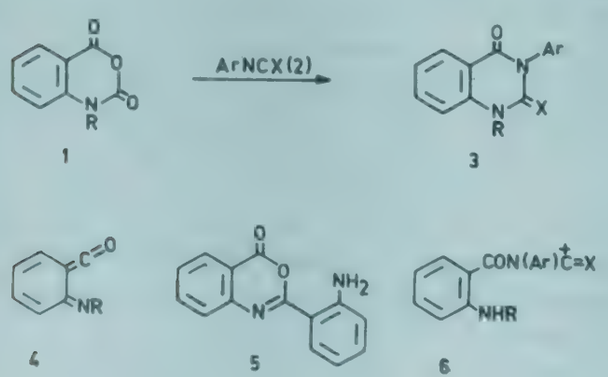
3-Aryl-(2-thio)-1H,3H-quinazolin-2,4-diones (**3**, R = H, CH_3, C_2H_5; X = O, S) have been obtained by the fusion of isatoic anhydrides (**1**, R = H, CH_3, C_2H_5) with aryliso(thio)cyanates (**2**, X = O, S).

Isatoic anhydride (**1**, R = H) on pyrolysis afforded 2-(2-aminophenyl)-3,1-benzoxazin-4-one (**5**), which was considered to arise from the Diels-Alder type reaction of an unisolable iminoketene intermediate (**4**, R = H)[1,2]. The postulated nature of this intermediate as a 4π heterodiene system prompted us to study the pyrolysis of isatoic anhydride (**1**, R = H) in the presence of reactive dienophiles to intercept **4**. As a prelude to testing the feasibility of such a scheme, the fusion of isatoic anhydrides (**1**; R = H, CH_3, C_2H_5) with aryliso(thio)cyanates (**2**, X = O, S) was studied (Scheme 1).

Thus, an equimolar mixture of **1** (R = H) and 4-chlorophenylisocyanate (**2**, Ar = 4-ClC_6H_4, X = O) was heated at 260°C for 2 hr and the cooled melt on recrystallisation yielded 3-(4-chlorophenyl-1H,3H-quinazolin-2,4-dione (**3b**), identical with an authentic sample[3]. Fusion of **1** (R = H) and 4-chlorophenylisothiocyanate (**2**, AR = 4-ClC_6H_4, X = S) led to **3b**. As an extension fusion of N-methyl- (**1**, R = CH_3) and N-ethyl- (**1**, R = C_2H_5) isatoic anhydrides with other aryliso(thio)cyanates (**2**, X = O, S) led in all cases to the corresponding 3-aryl-1H,3H-quinazolin-2,4-diones (**3**, X = O) and their 2-thio analogues (**3**, X = S) in 70-80% yield (Table 1).

The formation of **3** in the above reaction testifies that isatoic anhydrides (**1**) undergo a retro Diels-Alder type cleavage at high temperatures, diene component being an iminoketene (**4**). The latter readily interacts with 2π systems like aryliso(thio)cyanates (Scheme 1). Incidentally, the reaction provides an easy access to the title compounds (**3**)[4-9], some of



R	Ar	X
H	C_6H_5	O
CH_3	4-ClC_6H_4	S
C_2H_5	4-BrC_6H_4	
	4-$H_3CC_6H_4$	
	4-$H_3COC_6H_4$	

Scheme 1

Table 1 — 3-Aryl-(2-thio)-1H,3H-quinazolin-2,4-diones (**3a-u**)

Compound **3**	Ar	m.p. (°C) (lit. m.p.)
	X = O; R = H	
a	C_6H_5	268 (271)[3]
b	4-ClC_6H_4	270 (271)[3]
c	4-$H_3COC_6H_4$	248
	X = O; R = CH_3	
d	C_6H_5	252
e	4-ClC_6H_4	260
f	4-$H_3COC_6H_4$	249
	X = O; R = C_2H_5	
g	C_6H_5	246
h	4-ClC_6H_4	253
i	4-$H_3COC_6H_4$	237
	X = S; R = H	
j	C_6H_5	307 (307)[3]
k	4-ClC_6H_4	317 (317-19)[3]
l	4-BrC_6H_4	320 (314-15)[3]
m	4-$H_3CC_6H_4$	301 (303)[3]
	X = S; R = CH_3	
n	C_6H_5	310
o	4-ClC_6H_4	303
p	4-BrC_6H_4	309
q	4-$H_3CC_6H_4$	297
	X = S; R = C_2H_5	
r	C_6H_5	258
s	4-ClC_6H_4	259
t	4-BrC_6H_4	271
u	4-$H_3CC_6H_4$	262

[a]Melting points are uncorrected; [b]satisfactory analytical data were obtained: C ± 0.037, H ± 0.021, N ± 0.032.

which are not known in literature. The structures were assigned based on spectral data and by analogy. Isatoic anhydrides also react with **2** in polar media such as acetic acid and dimethylformamide to give **3a-u**, in 60-70% and 50-60% yields respectively possibly through the ionic intermediate (**6**).

3-*Aryl*-(2-*thio*)-1*H*,3*H*-*quinazolin*-2,4-*diones* (**3a-u**): (*a*) *Under thermal conditions*

A mixture of **1** (10 mmol) and aryliso(thio)cyanate (**2**, 10 mmol) was heated for 2 hr at 20°C above the melting point of the corresponding isatoic anhydride. The cooled pyrolysate on recrystallisation from methanol, yielded 3-aryl-(2-thio)-1H,3H-quinazolin-2,4-diones (**3a-u**). The yields were generally good (70-80%).

3d: IR(KBr): 1665, 1680 cm^{-1} (C=O); PMR (DMSO-d_6): δ 3.6 (*s*, 3H, $-NCH_3$), δ 7.3-8.3 (*m*, 9H, aromatic); MS *m/z* (relative intensity): 252 (M^+, 100), 133 (70), 119 (21), 118 (61), 105 (67), 104 (15), 90 (37), 64 (32).

3g: IR(KBr): 1665, 1680 cm^{-1} (C=O); PMR (DMSO-d_6): δ 1.3 (*t*, 3H, $-CH_2CH_3$), 4.8 (*q*, 2H, $-CH_2CH_3$), 7.2-8.2 (*m*, 9H, aromatic); MS *m/z* (relative intensity): 266 (M^+, 100), 147 (69), 119 (40), 118 (57), 104 (7), 90 (39), 64 (35).

3n: IR (KBr): 1665 (C=O), 1260 cm^{-1} (C=S); PMR (DMSO-d_6): δ 3.6 (*s*, 3H, $-NCH_3$), 7.3-8.3 (*m*, 9H, aromatic); MS *m/z* (relative intensity): 268 (M^+, 100), 135 (25), 133 (67), 118 (62), 105 (67), 104 (7), 90 (32), 64 (31).

3r: IR (KBr): 1665 (C=O), 1260 cm^{-1} (C=S); PMR) DMSO-d_6): δ 1.3 (*t*, 3H, $-CH_2CH_3$), 4.81 (*q*, 2H, $-CH_2CH_3$), 7.2-8.2 (*m*, 9H, aromatic); MS *m/z* (relative intensity): 282 (M^+, 100), 147 (75), 135 (21), 119 (69), 118 (65), 104 (9), 90 (36), 64 (25).

(*b*) *In dimethylformamide*

An equimolar mixture of an isatoic anhydride (**1**, 10 mmol) and aryliso(thio)cyanate (**2**, 10 mmol) in dimethylformamide (10 ml) was refluxed for 1 hr. Compounds (**3a-u**)) that separated on cooling the reaction mixture were filtered and recrystallised from methanol in 60-70% yields.

(*c*) *In acetic acid*

A mixture of an isatoic anhydride (**1**, 10 mmol) and aryliso(thio)cyanate (**2**, 10 mmol) in acetic acid (10 ml) was refluxed for 1 hr and the reaction mixture was left aside at room temperature for 4 hr. Compounds (**3a-u**) that separated were filtered and recrystallised from methanol in 60-70% yields except **3b, 3c, 3e, 3h** and **3i** which were obtained in almost 50% yields.

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Synthesis of Some New β-Lactams, 4-Thiazolidinones & Pyrazolines

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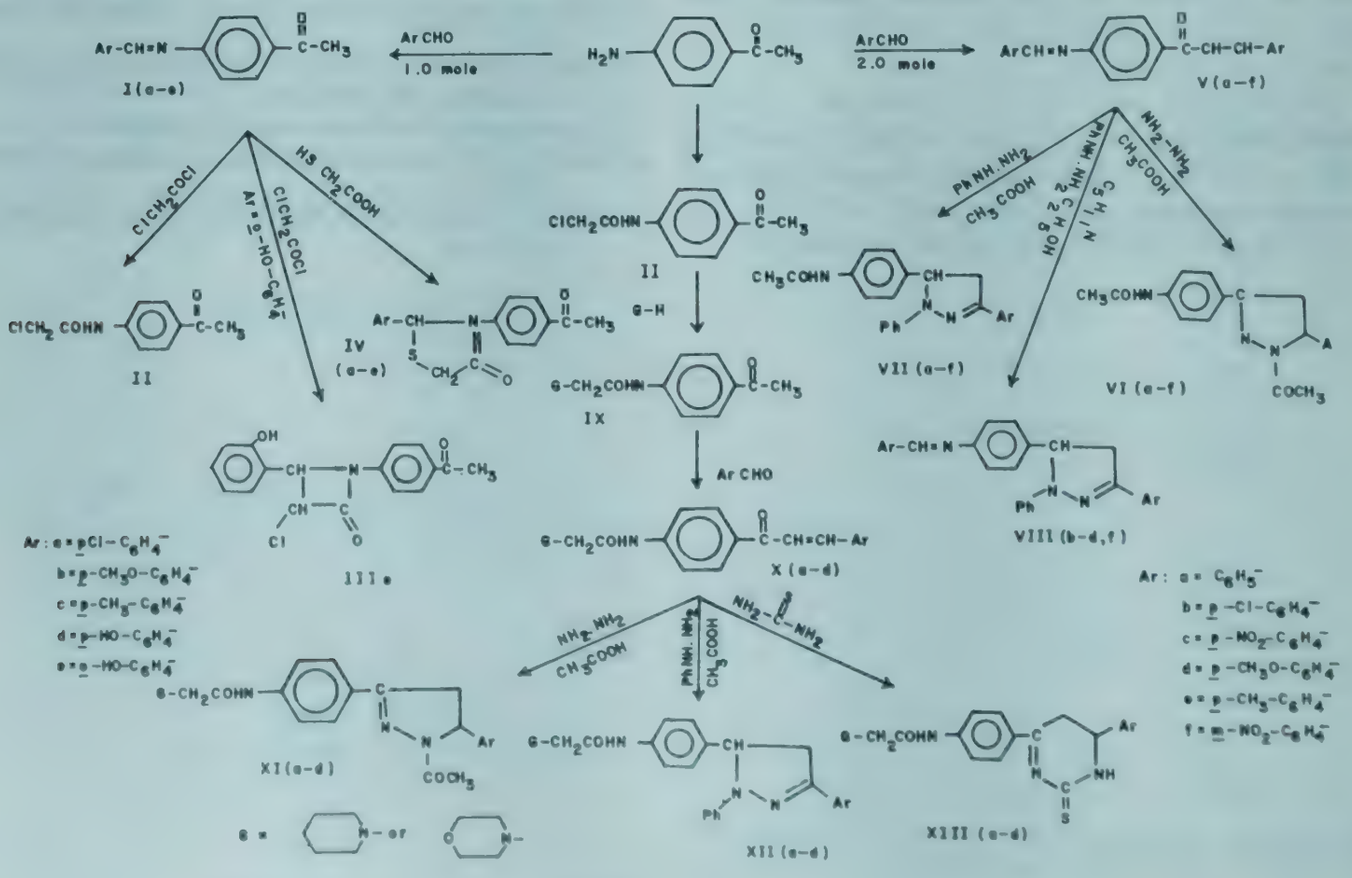
N-Arylidine-*p*-aminoacetophenone (I) and N-arylidine-4′-aminochalcones (V) have been converted into a series of substituted β-lactams (III) and 4-thiazolidinones (IV), and pyrazolines (VI, VII) respectively. *p*-Chloroacetamidoacetophenone (II) has also been converted into series of substituted 4′-piperidino/morpholinoacetoamidochalones (X) which undergo cyclization on treatment with hydrazine, phenylhydrazine or thiourea to pyrazolines (XI, XII) and pyrimidine-2-thiones (XIII) respectively. The antibacterial and antifungal activities of the compounds have been determined.

A large number of antibiotics such as pencillins, cephalosporins, nocardicins and thienamycins[1-6] bear a β-lactam ring. 4-Thiazolidinones find their application as local anaesthetics, anticonvulsant agents and as moderate tuberculostatic agents[7-13]. These reports prompted us to undertake the preparation of a number of hitherto unreported β-lactams, 4-thiazolidinones and pyrazolines and evaluation of their biological activity.

The required N-arylidine-*p*-aminoacetophenones (I) were prepared by the interaction of aromatic aldehydes and *p*-aminoacetophenone. The acetophenones Ia-d on reaction with chloroacetyl chloride following the method of Bose *et al.*[14] failed to give the expected β-lactams but resulted in hydrolytic chloroacetylation to give *p*-chloroacetamidoacetophenone (II). However, *o*-hydroxybenzylidineacetophenone (Ie) under these conditions underwent cyclocondensation with chloroacetyl chloride giving the corresponding β-lactam (III; Scheme 1) [IR: 1595 (C = O of monocylic β-lactam) and 3400 cm^{-1} (OH)]. The difference in cyclocondensation behaviour between the schiff bases Ie and Ia-d is probably due to hydrogen bonding in Ie.

4-Thiazolidinones (IVa-e; Table 1) were prepared by the reaction of I with mercaptoacetic acid [IR: 1600 cm^{-1} (CO of 4-thiazolidinone)].

Pyrazolines as a class of heterocyclic compounds have many medicinal applications as anaesthetics[15],



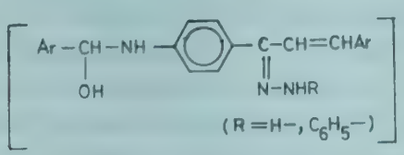
Scheme 1

Table 1—Characterization Data of 4-Thiazolidinones (IVa-e), 1-Acetylpyrazolines (VIa-f), 1-Phenylpyrazolines (VIIIa-f) and 5-(*p*-N-Arylideneaminophenyl)pyrazolines (VIIIb-d,f)

Compd	Ar	m.p.* °C	Yield (%)	Mol. formula†
IVa	C_6H_4Cl-*p*	154-55	67	$C_{17}H_{14}NO_2SCl$
IVb	$C_6H_4OCH_3$-*p*	140-42	52	$C_{18}H_{17}NO_3S$
IVc	$C_6H_4CH_3$-*p*	174-75	61	$C_{18}H_{17}NO_2S$
IVd	C_6H_4OH-*p*	148-50	55	$C_{17}H_{15}NO_3S$
IVe	C_6H_4OH-*o*	145-46	51	$C_{17}H_{15}NO_3S$
VIa	C_6H_5-	255-57	49	$C_{19}H_{19}N_3O_2$
VIb	C_6H_4Cl-*p*	290-92	54	$C_{19}H_{18}N_3O_2Cl$
VIc	$C_6H_4NO_2$-*p*	300-302	55	$C_{19}H_{18}N_4O_4$
VId	$C_6H_4OCH_3$-*p*	220-22	46	$C_{20}H_{21}N_3O_3$
VIe	$C_6H_4CH_3$-*p*	265-66	33	$C_{20}H_{21}N_3O_2$
VIf	$C_6H_4NO_2$-*m*	285-96	55	$C_{19}H_{18}N_4O_4$
VIIa	C_6H_5-	235-36	35	$C_{23}H_{21}N_3O$
VIIb	C_6H_4Cl-*p*	330-32	50	$C_{23}H_{20}N_3OCl$
VIIc	$C_6H_4NO_2$-*p*	208-89	55	$C_{23}H_{20}N_4O_3$
VIId	$C_6H_4OCH_3$-*p*	98-99	35	$C_{24}H_{23}N_3O_2$
VIIe	$C_6H_4CH_3$-*p*	120-22	46	$C_{24}H_{23}N_3O$
VIIf	$C_6H_4NO_2$-*m*	290-92	54	$C_{23}H_{20}N_4O_3$
VIIIb	C_6H_4Cl-*p*	177-78	27	$C_{28}H_{21}N_3Cl_2$
VIIIc	$C_6H_4NO_2$-*p*	165-67	33	$C_{28}H_{21}N_5O_4$
VIIId	$C_6H_4OCH_3$-*p*	100-102	25	$C_{30}H_{27}N_3O_2$
VIIIf	$C_6H_4NO_2$-*m*	95-96	34	$C_{28}H_{21}N_5O_4$

*Solvent used for crystallization were: Benzene-pet. ether (60-80°) for IVa-e and VIId, e; acetic acid for VIa-f, VIIa-c, f; ethanol for VIIIb, c; pet. ether (60-80°) for VIIId, f.
†Satisfactory elemental analyses were obtained for all the compounds.

anthelmentics[16], and inflamation reducting agents[17]. In the present investigation such compounds were prepared from N-arylidine-4′-aminochalcones (Va-f) which were obtained by the reaction of two mol of aromatic aldehydes with *p*-aminoacetophenone. The formation of 1-acetylpyrazolines (VI) and 1-phenylpyrazolines (VII) (Table 1) from V and hydrazines is believed to take place via 1,2- and 1,4-addition reactions as suggested earlier[18]. At the same time, the hydrolysis of azomethine group can take place with the formation of a tetrahedral carbinolamine intermediate which undergoes at least one-proton transfer before breaking down to the corresponding products.



The structures of the compounds VI and VII were established by elemental analyses and spectral data. Further support for the structures VI and VII came from the finding that all the aldehydes resulting from the hydrolysis of the imino group were detected by co-TLC with authentic samples. The forgoing structures were also established by their synthesis through an alternative route.

N-Arylideno-1-phenylpyrazolines (VIII; Table 1) were prepared by the normal route using ethanol as solvent and piperidine as catalyst. Their structures were established by elemental analyses and spectral data. All attempts to react compounds VIII using azomethine center to form β-lactams, thiazolidinones or triazines were unsuccessful, because of poor solubility of VIII in solvents generally employed for these reactions.

It is known that the introduction of an amido function in a molecule enhances its pharmacological action. Also, piperidine and morpholine derivatives fined their wide clinical application[19]. Thus, in the present study compound II was reacted with piperidine and morpholine to form IX which reacted with aldehydes affording 4′-piperidino/morpholino-acetoamidochalcones (Xa-d). These chalcones (X) reacted readily with hydrazine hydrate, phenylhydrazine and thiourea giving the pyrazolines (XI, XII) and pyrimidine-2-thiones (XII) (Table 2) respectively. The structures of X, XI, XII and XIII were established by elemental analyses and spectral data.

Table 2—Characterization Data of Chalcones (Xa-d), 1-Acetylpyrazolines (XIa-d), 1-Phenylpyrazolines (XIIa-d) and Pyrimidine-2-thiones (XIIIa-d)

Compd	Ar	G = Piperidino-			G = Morpholino-		
		m.p.C* °C	Yield (%)	Mol. formula†	m.p.‡ °C	Yield (%)	Mol. formula†
IX	—	105-7	95	$C_{15}H_{20}N_2O_2$	93-95	96	$C_{14}H_{18}N_2O_3$
Xa	C_6H_5-	170-72	45	$C_{22}H_{24}N_2O_2$	158-60	40	$C_{21}H_{22}N_2O_3$
Xb	C_6H_4Cl-*p*	255-56	69	$C_{22}H_{23}N_2O_2Cl$	208-9	62	$C_{21}H_{21}N_2O_3Cl$
Xc	$C_6H_4NO_2$-*p*	232-34	67	$C_{22}H_{23}N_3O_4$	213-15	50	$C_{21}N_{21}N_3O_5$
Xd	$C_6H_4OCH_3$-*p*	163-65	56	$C_{23}H_{26}N_2O_3$	144-45	45	$C_{22}H_{24}N_2O_4$
XIa	C_6H_5-	105-6	30	$C_{24}H_{28}N_4O_2$	190-92	30	$C_{23}H_{26}N_4O_3$
XIb	C_6H_4Cl-*p*	135-36	35	$C_{24}H_{27}N_4O_2Cl$	147-48	30	$C_{23}H_{25}N_4O_3Cl$
XIc	$C_6H_4NO_2$-*p*	180-82	50	$C_{24}H_{27}N_5O_4$	304-5	35	$C_{23}H_{25}N_5O_5$
XId	$C_6H_4OCH_3$-*p*	110-12	37	$C_{25}H_{30}N_4O_3$	95-96	33	$C_{24}H_{28}N_4O_4$
XIIa	C_6H_5-	193-95	40	$C_{28}H_{30}N_4O$	172-73	40	$C_{27}H_{28}N_4O_2$
XIIb	C_6H_4Cl-*p*	195-96	45	$C_{28}H_{29}N_4OCl$	120-22	55	$C_{27}H_{27}N_4O_2Cl$
XIIc	$C_6H_4NO_2$-*p*	125-26	47	$C_{28}H_{29}N_5O_3$	115-56	50	$C_{27}H_{27}N_5O_4$
XIId	$C_6H_4OCH_3$-*p*	80-82	42	$C_{29}H_{32}N_4O_2$	140-42	45	$C_{28}H_{30}N_4O_3$
XIIIa	C_6H_5-	155-57	30	$C_{23}H_{26}N_4OS$	197-200	32	$C_{22}H_{24}N_4O_2S$
XIIIb	C_6H_4Cl-*p*	180-82	32	$C_{23}H_{25}N_4OClS$	182-83	30	$C_{22}H_{23}N_4O_2ClS$
XIIIc	$C_6H_4NO_2$-*p*	255-56	35	$C_{23}H_{25}N_5O_3S$	210-11	36	$C_{22}H_{23}N_5O_4S$
XIIId	$C_6H_4OCH_3$-*p*	190-92	33	$C_{24}H_{28}N_4O_2S$	167-69	32	$C_{23}H_{26}N_4O_3S$

*Solvent used for crystallization were: toluene-pet. ether (60-80°) for IX, ethanol for Xa-d and XIIa-d, acetic acid-water for XIa-d for XIa-d and XIIIc; benzene-pet.-ether (60-80°) for XIIIa,b,d.

†Satisfactory elemental analyses were obtained for all the compounds.

‡Solvent used for crystallization were: Benzene for IX and XIIb-d; ethanol for Xa-d and XIa,b, XIIIa-d; acetic acid for XIc, XIIa; pet. ether (60-80°) for XId.

Microbiological screening

The compounds were tested for their antibacterial and antifungal activities. The results show that the starting materials (schiff bases Va-c) exhibit 30-70% activity against *Serratia* and *Bacillus* and 70% against *Micrococcus*. These compounds also show 50-70% activity against the fungi *Fusarium* and *Rhizoctonia*. When the schiff bases (V) are converted into the amidopyrazolines (VIa-c) they exhibit 30-50% activity against *Micrococcus* and *Bacillus* and 100% activity against *Fusarium* and *Rhizoctonia*. Thus, the activity of VI against *Micrococcus* and *Bacillus* is lower than that of the starting compounds (V).

Amidopyrazolines (VIIa-c) and pyrazolines (VIIIa-c) containing azomethine linkage show a higher activity ($\simeq$ 70%) against *serratia* and *Micrococcus*. However, this activity is maximum against *Fusarium* (50-70%) and *Rhizectonia* (100%).

The chalcones X showed about 30% to negative activity against bacteria and fungi, except morpholinochalcones (Xc,d) which exhibit about 70% activity against *Penicillium natatum, cladosporium* and *Aspergillus flavus*.

On the other hand, when the chalcones X are changed into pyrazolines their microbiological activity is modified. The experimental data show that the morpholinoacetamidopyrazolines (XIa-d) and pyrimidinethiones (XIIIa-d) exhibit 70-100% activity against most of the bacteria and fungi used in this work.

The only β-lactam which does not show antibacterial activity is IIIe, but it exhibits 70% activity against *Penicillium natatus*. The thiazolidinone IVa show 50-70% activity against *E. coli* and *Aspergillus flavus*.

Melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded on a Pye-Unicam SP 1200 spectrometer in KBr discs. Purity of all the compounds and progress of the reactions were determined by TLC.

N-Arylidine-p-aminoacetophenones (Ia-e)

These compounds were prepared by melting an equimolar mixture of *p*-aminoacetophenone and substituted aromatic aldehydes on a water-bath till resolidified. The solid product was crystallized from ethanol to get I. The melting points of I coincided with those given in literature[20].

1-(4-p-Acetophenyl)-3-chloro-4-(o-hydroxyphenyl)azetidine-2-one (IIIe)

It was prepared according to the method of Bose *et al.*[14], yield 44%, m.p. 140-42°C (Found: C, 64.1;

H, 4.3; N, 4.2; Cl, 11.3. Calc. for $C_{17}H_{14}NO_3Cl$: C, 64.7; H, 4.4; N, 4.4; Cl, 11.3%).

3-(4-Acetophenyl)-2-arylthiazolidin-4-ones (IVa-e)

These compounds were prepared following the method of Surry *et al.*[8] Their characterization data are given in Table 1.

N-Arylidene-4′-aminochalcones (Va-f)[20]

These compounds were prepared by heating a mixture of *p*-aminoacetophenone (1.0 mol) and aromatic aldehydes (2.0 mol) in ethanol in the presence of 3 ml of 20% NaOH. The product was crystallized from an appropriate solvent.

1-Acetyl-3-(4-acetoamidophenyl)-5-aryl-2-pyrazolines (VIa-f) and 5-(4-acetoamidophenyl)-3-aryl-1-phenyl-2-pyrazolines (VIIa-f)

A mixture of N-arylidene-4′-aminochalcone (0.003 mol) and hydrazine hydrate (3 ml, 24%; 0.1 mol) or phenylhydrazine (1 mol, 0.1 mol) in acetic acid (30 ml) was refluxed for 10 hr and the product crystallized from an appropriate solvent. The Characterization data of VI and VII are given in Table 1.

5-(p-N-Arylidineaminophenyl)-3-aryl-1-phenyl-2-pyrazolines (VIIIb-d, f)

A mixture of V (0.003 mol), phenylhydrazine (0.01 mol) in ethanol and two drops of piperidine was refluxed for 6 hr and the reaction product crystallized from a proper solvent. The characterization data of VIII are given in Table 1.

4′ Piperidino/morpholinoacetamido-chalcones (Xa-d)

These compounds were prepared by heating an equimolar mixture of 4-piperidino/morpholinoacetamidoacetophenone (IX) and aromatic aldehydes in ethanol in the presenc eof 3 ml of 4% KOH. The product was crystallized from appropriate solvent. The characterization data of X are given in Table 2.

1-Acetyl-5-aryl-3-(4′-piperidino/morpholino-acetamidophenyl)- and 3-aryl-1-phenyl-5-(4′-piperidino/morpholino-acetoamidophenyl-2-pyrazolines (XIa-d and XIIa-d)

These compounds were prepared by the reaction of X with hydrazine hydrate or phenylhydrazine in acetic acid as described above. Their characterization data are given in Table 2.

6-Aryl-4-(4′-piperidino/morpholino-acetamidophenyl)-1, 2, 5, 6-tetrahydropyrimidine-2-thiones (XIIIa-d)

A mixture of 4′-piperidino/morpholino-acetamidochalcones (0.002 mol), thiourea 0.3 g (0.003 mol) and KOH (1.09) in ethanol (50 ml) and water (3 ml) was refluxed for 15 hr. The reaction products were crystallized from appropriate solvents. The characterization data of XIII are given in Table 2.

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Reaction of 1,2,3-Benzoxathiazine-2,2-dioxides with 1,3-Diphenylnitrilimine: Synthesis of a New Heterocyclic System

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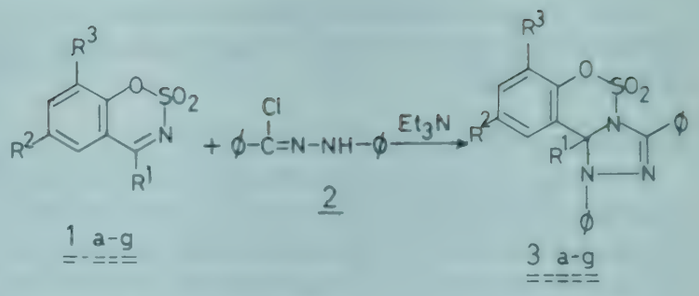
A new class of heterocyclic system (**3a-g**) has been synthesized by reacting 1,3-diphenylnitrilimine, generated *in situ*, with 1,2,3-benzoxathiazine-2,2-dioxides (**1a-g**).

We report herein an interesting cycloaddition reaction, which has led to a new class of heterocycle. Thus, 1,2,3-Benzoxathiazine-2,2-dioxides (**1a-g**) undergo cycloaddition reaction with 1,3-diphenylnitrilimine (DPN) generated *in situ* to afford a new class of interesting heterocycles (**3a-g**). The structure of the heterocycles (**3a-g**) are based on spectral data (PMR, mass) and elemental analyses (Table 1).

3a, the representative compound of the series, exhibits IR absorption bands at 1380 and 1150 cm^{-1}. In the PMR spectrum all the protons show up as a complex multiplet in the aromatic region δ 6.4-8.2. There are no signals corresponding to benzylic proton in the region δ 5.5-6.0. These data support the structure (*vide* scheme 1) assigned to the cycloadduct. The mass fragmentation data are also in agreement with the above structure. Benz-N-phenylhydrazidoyl chloride (**2**), 3,5-dibromosalicylaldehyde and 5-chlorosalicylaldehyde were prepared by the procedure described in the literature[1-3].

1,2,3-Benzoxathiazine-2,2-dioxides (**1a-g**) were



a : $R^1 = R^2 = R^3 = H$
b : $R^1 = R^3 = H$; $R^2 = Br$
c : $R^1 = H$; $R^2 = R^3 = Br$
d : $R^1 = R^3 = H$; $R^2 = Cl$
e : $R^1 = H$; $R^2 = R^3 = I$
f : $R^1 = CH_3$; $R^2 = R^3 = H$
g : $R^1 = \phi$; $R^2 = R^3 = H$

SCHEME 1

prepared as follows: To a stirred solution of the 2-hydroxy compounds (0.046 mol) in toluene (40 ml) at 100-105° was added chlorosulphonyl isocyanate (4 ml, 0.046 mol) in toluene (5 ml) during 20 min. Stirring was continued for 3 hr at the same temperature, the solvent was distilled off under diminished pressure and the residue diluted with ice-cold water (50 ml) to obtain a solid which was filtered, washed with water and recrystallized from ethanol.

Reaction of 1,2,3-*benzoxathiazine*-2,2-*dioxides with benz-N-phenylhydrazidoyl chloride* (**2**): *Formation of* **3a-g**

Dry triethylamine (0.3 ml) was added to a stirred solution of **1a-g** (0.001 mol) and benz-N-

Table 1—Characterization Data of Tricyclic Compounds (**3a-g**)

Compd (3)	R^1	R^2	R^3	m.p. °C	Yield (%)	Mol. formula*
a	H	H	H	155	95	$C_{20}H_{15}N_3O_3S$
b	H	Br	H	200	82	$C_{20}H_{14}BrN_3O_3S$
c	H	Br	Br	210	85	$C_{20}H_{13}Br_2N_3O_3S$
d	H	Cl	H	200	82	$C_{20}H_{14}ClN_3O_3S$
e	H	I	I	240	85	$C_{20}H_{13}I_2N_3O_3S$
f	CH_3	H	H	180	86	$C_{21}H_{17}N_3O_3S$
g	C_6H_5	H	H	190	87	$C_{26}H_{19}N_3O_3S$

*All the compounds gave satisfactory elemental analyses.

phenylhydrazidoyl chloride (**2**, 0.203 g, 0.001 mol) in dry benzene (10 ml). The solution was stirred for 36 hr at 50-60°, filtered to remove the solid triethylamine hydrochloride and the filtrate evaporated to yield **3a-g** as crude solids. These were purified by passing their solutions in benzene through a silica gel column.

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Fusion of Aroylhydrazines with Acids—A New Synthesis of 2,5-Diaryl-1,3,4-oxadiazoles

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Aroylhydrazines and aromatic acids when heated together at 240°C for 6 hr yield 2,5-diaryl-1,3,4-oxadiazoles (V) in one step. Permanganate oxidation of 1-aroyl-2-arylidenehydrazines is also shown to be a superior method for preparing 1,3,4-oxadiazoles (V).

2,5-Diaryl-1,3,4-oxadiazoles have found a variety of uses as pesticides, pharmaceuticals, colour developers, stabilisers in photography, dyes, protectives against UV radiation, liquid solution scintillators and thermostable polymers[1]. Consequently, a number of synthetic approaches to the 1,3,4-oxadiazole system have been developed and most of these involve the use of hydrazine or its derivative, as a source of two contiguous nitrogen atoms, and a variety of cyclising reagents[1-4].

We report herein a facile and new synthesis of 2,5-diaryl-1,3,4-oxadiazoles (V) which obviates the use of any cyclisation reagent. The method involves heating a mixture of aroylhydrazines and aromatic acids and isolating the product from the melt. For example, a mixture of benzoylhydrazine (I, R = C_6H_5, 10 mmol) and benzoic acid (II, R′ = C_6H_5, 20 mmol) was heated at 240° for 6 hr. The mixture melted first and solidified around 160-70° and remelted as the temperature increased to 200°. After cooling, the fused material was treated with 10% aq. sodium bicarbonate (100 ml). The insoluble product was filtered, washed repeatedly with water (5 × 20 ml) and recrystallised from a suitable solvent to give Va.

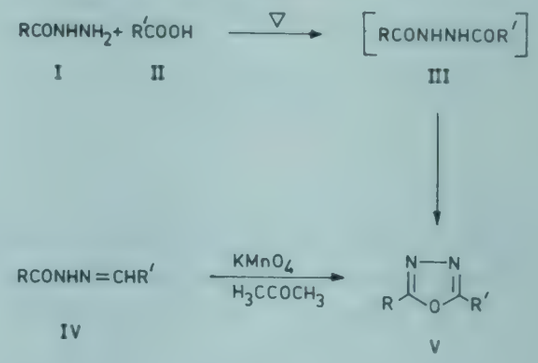

Table 1—2,5-Diaryl-1,3,4-oxadiazoles (V)

Compound (V)	R	R′	m.p.°C (lit.)	Yield (%)	
				Pyrolysis	Permanganate oxidation
a	C_6H_5	C_6H_5	138[a*] (140)[14]	51	79
b	C_6H_5	4-ClC_6H_4	160[b+d] (158)[15]	46	81
c	C_6H_5	4-$O_2NC_6H_4$	207[c] (209)[16]	48	82
d	C_6H_5	4-$H_3CC_6H_4$	148[a]	52	76
e	C_6H_5	3-C_5H_4N	130[a+c] (132)[15]	45	78
f	C_6H_5	2-C_4H_3O	154[a+e]	53	75
g	4-ClC_6H_4	4-ClC_6H_4	238[d] (245)[14]	50	80
h	4-$O_2NC_6H_4$	4-ClC_6H_4	219[b]	48	78
i	4-$H_3CC_6H_4$	4-$H_3CC_6H_4$	187[c] (176)[17]	55	76
j	4-$H_3COC_6H_4$	4-$H_3COC_6H_4$	160[c] (160)[14]	51	75
k	4-$H_3CC_6H_4$	4-ClC_6H_4	202[c] (206)[15]	50	81
l	4-$H_3COC_6H_4$	4-$H_3CC_6H_4$	150[a] (148)[16]	48	79

*Recrystallisation solvent : (a) benzene; (b) methanol; (c) ethanol; (d) acetone; and (e) pet. ether.

The above reaction when carried out in 1:1 molar ratio of the reactants also afforded V but in reduced yield. This method was extended to aroylhydrazines and substituted aromatic acids and in all the cases, the corresponding 2,5-diaryl-1,3,4-oxadiazoles (V) were isolated in 50-55% yields (Table 1).

When the heating was carried out at 150° the product formed was identified as 1,2-diaroylhydrazine (III) which could independently be converted into 2,5-diaryl-1,3,4-oxadiazole (V) by raising the temperature 240°. This proves the intermediacy of III. The mechanism of thermally-induced amide bond formation-cum-dehydrative heterocyclisations have earlier been reported from our laboratories[5]. The possibility of self-catalysis by the acids has been eliminated by carrying out the reaction of I and II in diphenyl ether and isolating the oxadiazoles (V), albeit in low yields (38%).

2,5-Diaryl-1,3,4-oxadiazoles (V) obtained presently were fully characterised by direct comparison with authentic samples obtained by oxidative cyclisation of 1-aroyl-2-arylidenehydrazines (IV) in the presence of potassium permanganate. For example to a solution of 1-aroyl-2-arylidenehydrazine (1 mmol) in acetone (50 ml), solid potassium permanganate (1 g) was added and the reaction mixture refluxed on a steam-bath for 8 hr. Further quantities of permanaganate were added to the boiling solution until the pink colour of the solution persisted and boiling was continued for 1 hr more. The reaction mixture was filtered, the filtrate concentrated, the residue taken in water, treated with aq. sodium sulphite (20 ml), extracted with chloroform (3 × 50 ml) and chloroform extract dried (Na_2SO_4). Removal of the solvent followed by recrystallisation yielded V.

A number of oxidising agents like chlorine in carbon tetrachloride[6], bromine in glacial acetic acid[7–11], sodium hypobromite[7], sodium salt of N-chlorocarbamate[12] and iodine in presence of silver salts[13] have been reported for this purpose. But, we find that potassium permanganate in acetone is a superior oxidising agent since the yields are much better (~ 80%) and the reaction conditions are milder. Incidentally, the use of potassium permanganate in the oxidation of 1-aroyl-2-arylidenehydrazines (IV) to V is reported for the first time.

In conclusion, the easy accessibility of the starting materials, high yields of the products and simplicity of the isolation procedure render these two methods superior for preparing 2,5-diaryl-1,3,4-oxadiazoles.

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Vilsmeier Reaction on Some Alkyl-1,4-cyclohexadienes

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Vilsmeier reaction on five alkyl-1,4-cyclohexadienes (I – V) has been studied. The structures of the resulting benzenedi- and tricarboxaldehydes (VII – XIII) have been assigned on spectral and elemental analyses data.

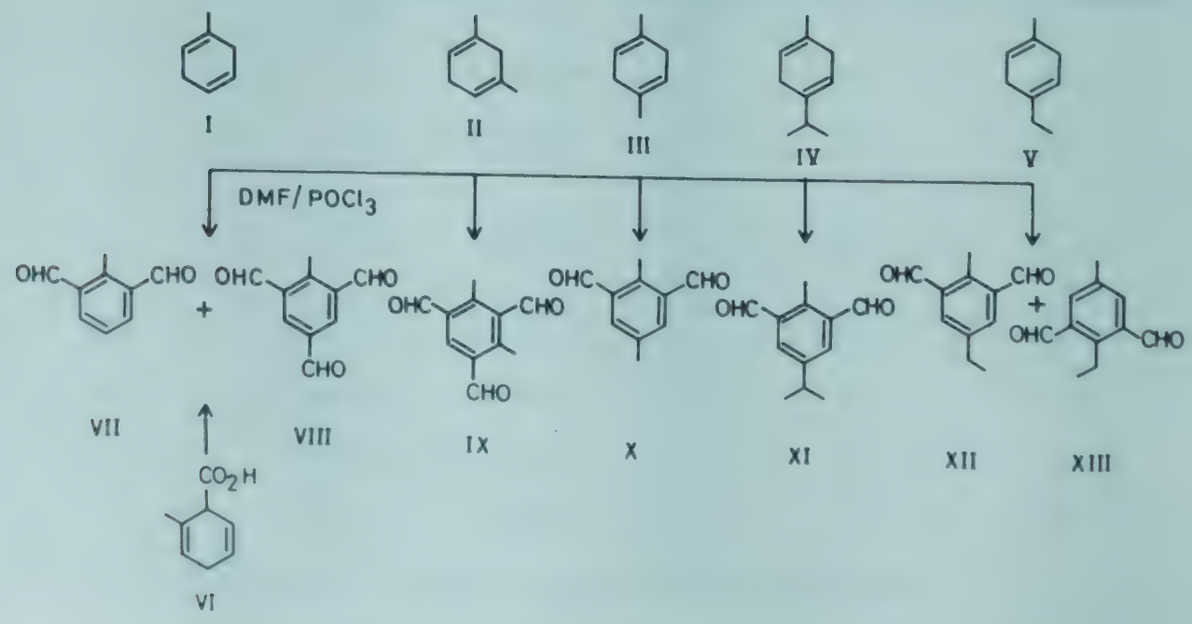
In extension of our recent investigations on the Vilsmeier reaction on methoxy[1]- and carboxy[2]-1,4-cyclohexadienes, we report in this note the results of our investigations on the Vilsmeier reaction[1-3] on the known alkyl-1,4-cyclohexadienes (I-V).

1-Methyl-1,4-cyclohexadiene[4] (I) on Vilsmeier reaction afforded a mixture containing 2-methylbenzene-1,3-dicarboxaldehyde (VII) and 2-methylbenzene-1,3,5-tricarboxaldehyde (VIII), separated by column chromatography (silica gel, pet. ether/ethyl acetate), and shown to be identical with the products obtained[2] by the Vilsmeier reaction on 1-carboxy-2-methyl-2,5-cyclohexadiene (VI). 1-5-Dimethyl-1,4-cyclohexadiene[4] (II) on similar reaction gave 2,4-dimethylbenzene-1,3,5-tricarboxaldehyde (IX), the structure of which was confirmed by its PMR spectrum. 1,4-Dimethyl-1,4-cyclohexadiene[4] (III) furnished 2,5-dimethylbenzene-1,3-dicarboxaldehyde (X). 1-Methyl-4-isopropyl-1,4-cyclohexadiene[4] (IV) on Vilsmeier reaction gave *p*-cymene-2,6-dicarboxaldehyde (XI), while that on 2,5-dihydro-4-ethyltoluene[4] (V) produced an oils mixture, inseparable by column or TLC, consisting of 5-ethyl-2-methylbenzene-1,3-dicarboxaldehyde (XII) and 2-ethyl-5-methylbenzene-1,3-dicarboxaldehyde (XIII) in 2:1 ratio (PMR). The absence of attack of the Vilsmeier complex on the adjacent positions of the isopropyl group in compound IV and the predominance of the product XII in the reaction on V indicates as expected the enhanced reactivity at sterically more accessible sites.

The melting points reported are uncorrected. Pet. ether refers to the fraction, b.p. 60-80°C.

Vilsmeier reaction on 1-*methyl*-1,4-*cyclohexadiene* (*I*)[4]: *General procedure*

To DMF (14.6 g, 200 mmol) taken in a glass tube (15 cm × 3 cm) equipped with a teflon coated pellet and magnetic stirring arrangement, $POCl_3$ (12.24 g, 80 mmol) was added under stirring at 10° during 1.5 hr. To the Vilsmeier complex thus prepared was added I[4] (1.8 g, 20 mmol) in one lot at room temperature, the tube immersed in liquid nitrogen bath and sealed under reduced pressure. The sealed tube was allowed to attain room temperature and placed in an oil-bath maintained at 80-90°C. The contents of the tube were thoroughly mixed by frequent shaking until it became homogeneous (20 hr). The tube was



cooled, opened carefully and the contents poured into ice-cold aq NaOAc (20%, 100 ml). The complex was decomposed by stirring for 1 hr at room temperature. The product was extracted with ether (4 × 50 ml). The combined ethereal phase was washed with aq Na_2CO_3 (10%), brine, dried (Na_2SO_4) and the solvent removed. The crude product was passed through a column of silica gel. Elution with pet. ether-ethyl acetate (10:1) gave VII (0.07 g, 3%), m.p. 78-80° (pet. ether) (lit.[2] m.p. 78-80°), identical (IR and PMR) with VII obtained earlier[2]. Further elution of the column with pet. ether-ethyl acetate (10:2) gave VIII (0.28 g, 9%), m.p. 138-40° (pet. ether-chloroform) (lit.[2] m.p. 138-40°), identical (IR and PMR) with VIII obtained earlier[2].

2,4-*Dimethylbenzene*-1,3,5-*tricarboxaldehyde* (IX)

Vilsmeier reaction on II[4] (2.1 g, 20 mmol) gave IX (0.3 g, 9%), m.p. 125-26° (pet. ether-ethyl acetate); IR (nujol): 1680 cm^{-1}; PMR ($CDCl_3$): δ 2.83 (6H, *s*, 2 × Ar − CH_3), 8.33 (1H, *s*, Ar − *H*), 10.33 (2H, *s*, C_1 − and C_5 − CHO), and 10.66 (1H, *s*, C_3 − CHO) (Found: C, 69.5; H, 5.4. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.3%).

2,5-*Dimethylbenzene*-1,3-*dicarboxaldehyde* (X)

Vilsmeier reaction on III[4] (2.1 g, 20 mmol) gave X (0.35 g, 10%), m.p. 112° (pet. ether-ethyl acetate); IR (nujol): 1690; PMR ($CDCl_3$): δ 2.6 (3H, *s*, C_5 − CH_3), 2.93 (3H, *s*, C_2 − CH_3) 7.8 (2H, *s*, 2 × Ar − H) and 10.36 (2H, *s*, 2 × CHO) (Found: C, 73.9; H, 6.1. $C_{10}H_{10}O_2$ requires C, 74.1; H, 6.2%).

p-Cymene-2,6-*dicarboxaldehyde* (XI)

Vilsmeier reaction on IV[4] (2.7 g, 20 mmol) gave XI (0.38 g, 10%), m.p. 75° (pet. ether-ethyl acetate); IR (nujol) 1675; PMR ($CDCl_3$): δ 1.3 (6H, *d*, *J* = 8 Hz, CH_3CHCH_3), 2.93 (3H, *s*, Ar − CH_3), 3.03 (1H, *m*, CH_3CHCH_3), 7.9 (2H, *s*, 2 × Ar − H) and 10.4 (2H, *s*, 2 × CHO) (Found: C, 75.4; H, 7.4. $C_{12}H_{14}O_2$ requires C, 75.8; H, 7.4%).

Vilsmeier reaction on 4-*ethyl*-1-*methyl*-1,4-*cyclohexadiene* (V)

Subjecting V[4] (2.4 g, 20 mmol) to Vilsmeier reaction as described in the general procedure gave an oily product (XII + XIII, 2:1) (0.3 g, 9%); IR (neat): 1680; PMR (CCl_4) (a) peaks corresponding to XII: δ 1.23 (3H, *t*, *J* = 8 Hz, CH_2CH_3), 2.7 (2H, *q*, *J* = 8 Hz, CH_2CH_3), 2.9 (3H, *s*, Ar − CH_3), 7.73 (2H, *s*, 2 × Ar − H) and 10.3 (2H, *s*, 2 × CHO): (b) Peaks corresponding to XIII: 1.23 (3H, *t*, *J* = 8 Hz, CH_2CH_3), 2.4 (3H, *s*, Ar − CH_3), 3.36 (2H, *q*, *J* = 8 Hz, CH_2CH_3), 7.73 (2H, *s*, 2 × Ar − H) and 10.3 (2H, *s*, 2 × CHO).

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Two New Flavones from *Ardisia floribunda* Wall in Roxb.

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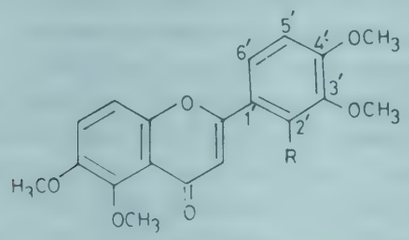
Two new flavones have been isolated from *Ardisia floribunda* Wall in Roxb (Myrsinaceae) and characterized as 5, 6, 3′, 4′-tetramethoxyflavone (I) and 5, 6, 2′, 3′, 4′-pentamethoxyflavone (II) on the basis of chemical transformation and spectral data (IR, UV, PMR and mass).

The isolation of two antitubercular phenols ardisinol-I and ardisinol-II from *Ardisia japonica*[1] and earlier reports on the constituents of chinese drug Kai-hochien (*Ardisia hortorum*)[2] promted us to investigate other species of *Ardisia*. Isolation of quinones[3-7], flavan[6], triterpenoids[3,8,9] and phenols[2,10] have been reported from different *Ardisia* species. We now report the isolation and structure elucidation of two new flavones from *Ardisia floribunda*.



I, R=H
II, R=OCH_3

The dried twigs of *Ardisia floribunda* (1 kg), procured from Dehradun and identified by Mr Kunwar Naresh Bahadur, Botany Division, Forest Research Institute, Dehradun, were cut into pieces and extracted with ethanol. The crude product (0.7 g) on solvent fractionation followed by column chromatography over silica gel using benzene as eluant gave a mixture of β-sitosterol and campestrol. Further elution afforded the chromatographically homogeneous compounds Af-2 and Af-1 successively.

The compound Af-1 (m.p. 171-72°) crystallized from chloroform-methanol as white crystals (50 mg). It analysed for $C_{19}H_{18}O_6$ (M^+ 342) and gave orange colour with Zn-HCl and Mg-HCl, and negative test with ethanolic ferric chloride; R_f 0.81 (yellowish blue fluorescence in UV light) in chloroform-ethyl acetate (9 : 1). It showed UV absorptions at 248.7 and 327.4 nm in chloroform and an IR (KBr) band at 1645 cm^{-1} for the carbonyl group. Its 60 MHz PMR spectrum in $CDCl_3$ exhibited singlets at δ 3.93 (3H), 3.95 (3H) and 3.96 (6H) assignable to methoxyl protons at 5, 6, 3′ and 4′-positions of the flavone. In the aromatic region there appeared a singlet at δ 6.61 for H-3, an *ortho*-coupled doublet (J = 9 Hz) at 7.00 for H-5′, a *meta*-coupled doublet (J = 2.5 Hz) at 7.36 for H-2′, an *ortho*-, *meta*-coupled *dd* (J = 9.0 and 2.5 Hz) at 7.56 for H-6′ and a singlet at 7.30 for H-7 and H-8. The first and last signals agree well with those of other 5,6-substituted flavones[11] for the same protons (Table 1). The mass spectrum of Af-I displayed $M^{+\cdot}$ at *m/z* 342, and the diagnostic fragments at 327 (M − 15), 312 (M − 30), 297 (M − 30 − 15), 282 (M − 2 HCHO or M − 4 Me), 165 (M − 136 − 41) and 137 (M − 165 − 41 − H). Therefore, Af-1 was assigned the structure as 5, 6, 3′, 4′-tetramethoxyflavone (I) which has been isolated from a natural source for the first time. However, a synthetic compound with same structure and m.p. 179-81° has been reported[12].

Table 1—Chemical Shifts of A and B Ring Protons of 5,6- and 5,7-Substituted Flavones in $CDCl_3$

Methoxyflavone	Chemical shift (δ, ppm) H-6 (*d*; J = 2 Hz)	H-8 (*d*; J = 2 Hz)	H-7,8 (*s*)	H-3 (*s*)
5,6,3′,5′-Tetramethoxyflavone[11]			7.40	6.65
5,6,3′-Trimethoxyflavone[11]			7.30	6.63
Af-1 (I)			7.30	6.61
Af-2 (II)			7.26	6.83
5,7,3′,4′-Tetramethoxyflavone[13]	6.35	6.58		6.58
5,7,2′,4′-Tetramethoxyflavone[14]	6.36	6.50		6.95
5,7,3′,4′,5′-Pentamethoxyflavone[13]	6.38	6.56		6.72

The compound Af-2 (m.p. 124-25°) crystallized from chloroform-methanol as white crystals (30 mg); R_f 0.83 (yellow fluorescence in UV light) in chloroform-ethyl acetate (9 : 1). It analysed for $C_{20}H_{20}O_7$ (M^+ 372) and gave an orange colour with Mg-HCl and Zn-HCl, and a negative test with ethanolic ferric chloride, indicating it to be a fully methylated flavone. It showed UV absorptions at 270 and 330 nm in chloroform and a sharp IR (KBr) band at 1645 cm^{-1} due to carbonyl function. Its 100 MHz PMR spec-

trum in $CDCl_3$ exhibited signals for five aromatic protons and fifteen methoxy protons. The methoxy protons appeared as singlets at δ 3.90 (3H), 3.93 (6H), 3.94 (3H) and 3.96 (3H). The *ortho*-coupled doublets at δ 6.78 (J = 9 Hz) and 7.50 (J = 9 Hz) were assigned to the aromatic protons H-5′ and H-6′, respectively. The singlet at δ 6.83 was assigned to H-3 and another singlet integrating for two protons appearing at 7.26 was assigned to H-7, 8 on the basis of the data given in Table 1. The mass spectrum of Af-2 displayed $M^{+\cdot}$ at *m/z* 372 and diagnostic fragments at 357(M − 15), 342(M − 30), 327(M − 45), 312(M − 30 − 30), 299, 284, 256, 177 and 149. The compound Af-2 was characterized as 5, 6, 2′, 3′, 4′-pentamethoxyflavone (II) which has been isolated for the first time from a natural source. The work on its synthesis is in progress.

We are thankful to Prof. N Kawano, Faculty of Pharmaceutical Sciences, Nagasaki University, Japan for PMR and mass spectra and to Prof. M S Ahmad, Chairman, Department of Chemistry, A M U, Aligarh for providing necessary facilities.

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Rubonic Acid, a New Triterpene Acid from *Rubus moluccanus*

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Rubonic acid, a new pentacyclic triterpene acid, isolated from the ethanolic extract of the defatted whole plant of *Rubus moluccanus*, has been formulated as 3,7-diketo-olean-12-ene-28-oic acid on the basis of spectral (IR, UV, PMR and mass) and chemical evidences.

In continuation of earlier work on the chemical constituents of different species of genus *Rubus*[1-3], we report herein the isolation and structure elucidation of yet another new pentacyclic triterpene acid, rubonic acid from the whole plant of *Rubus moluccanus*.

Air-dried whole plant of *R. moluccanus* was defatted with pet ether (60-80°) for 36 hr and then extracted with ethanol. The crude acid, obtained from the ethanolic extract by treatment with 3% aq alkali followed by acidification with HCl was esterified with ethereal diazomethane at 0°. The residue obtained after usual work-up was taken up in $CHCl_3$ and subjected to column chromatography over alumina. Elution with benzene gave the rubusic acid methyl ester which was crystallised from benzene-pet ether, m.p. 215-17°, identical with an authentic sample[4] (m.p., m.m.p., Co—IR). Further elution of the column with benzene-$CHCl_3$ afforded rubonic acid methyl ester which crystallised from benzene as colourless crystals, m.p. 256-57°. It was found TLC homogeneous. Rubonic acid methyl ester analysed for $C_{31}H_{46}O_4$.

Methyl rubonate (II) on hydrolysis with ethanolic alkali regenerated pure rubonic acid (I), $C_{30}H_{44}O_4$, crystallised from methanol-chloroform, m.p. 282-83°. This acid gave positive Liebermann-Burchard test for triterpene. The IR spectrum of methyl rubonate in KBr displayed peaks at 1740 and 1705 cm^{-1} for a carbomethoxy group and 6-membered ketone respectively. Methyl rubonate gave positive Zimmermann colour reaction confirming the presence of a keto function at C-3 in the triterpene skeleton. The methyl rubonate could not be reduced with potassium borohydride under normal conditions but under drastic conditions (36 hr refluxing with KBH_4 followed by column chromatography over silica gel using benzene-$CHCl_3$ as eluent) it gave the diol ester (III), $C_{31}H_{50}O_4$, which crystallised from chloroform-pet. ether, m.p. 216-17°. The diol ester (III) was found to be identical in all respects (m.p., m.m.p., co—IR) with methyl canthate which is 3,7-dihydroxy-olean-12-one-28-oic acid. Compound (III) on acetylation (Ac_2O/Py, room temperature) gave the diacetate (IV), $C_{35}H_{54}O_6$, which crystallised from chloroform-benzene, m.p. 194-95°. The IR spectrum of IV in KBr exhibited peaks at 1735 and 1260 cm^{-1} for acetoxy and at 1720 cm^{-1} for carbomethoxy and no peak in the OH region. This indicated that methyl rubonate contained two carbonyl functions.

Methyl rubonate (II) did not exhibit any UV absorption maxima for α- or β-diketone. Thus one of the carbonyl functions must be situated in a ring other than ring-A of the triterpene skeleton. In the mass spectrum of methyl rubonate (M^+ at *m/z* 482), the most abundant ions at *m/z* 262 and 203 could be assigned to fragments *a* and *b* (Scheme 1) on analogy[6]. An ion at *m/z* 219 was assigned to fragment *c*. The observations revealed that the second carbonyl group, other than that at C-3, was situated in ring-B. Thus the second carbonyl in methyl rubonate (II) must be either at C-6 or C-7 in ring-B.

The PMR spectrum of methyl rubonate in $CDCl_3$ displayed sharp singlets at δ 0.72(3H), 0.80(3H), 0.83(3H), 0.98(6H), 1.04(3H) and 1.12(3H) for seven tertiary methyl groups indicating methyl rubonate to be an oleanane derivative rather than an ursane derivative. That the methyl rubonate belonged to the oleanene series was evident from the appearance of multiplet centered around δ 2.84 for C-18 proton (axial) instead of a doublet exhibited by members of the ursene series[7-9]. This was further confirmed by the fact that on refluxing diacetyl methyl rubonate (IV) with SeO_2 in acetic acid for 3 hr, a heteroannular diene was obtained as a gummy mass, which exhibited in its UV spectrum maxima at 244, 253 and 263 nm, characteristic of $\Delta^{11,12,13-18}$ diene of the oleanene series[10-12]. Ursane derivatives having 12, 13 double bond are unaffected under this condition[13,14]. There was a triplet centered at δ 5.31 (J = 3.5 Hz) for the C-12 olefinic proton. The presence of C-28 carbomethoxy group was confirmed by the appearance of sharp singlet at δ

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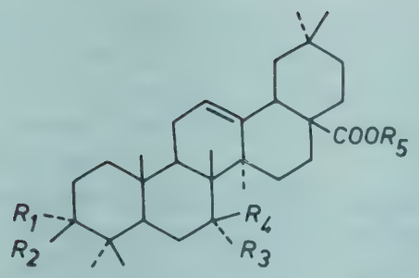
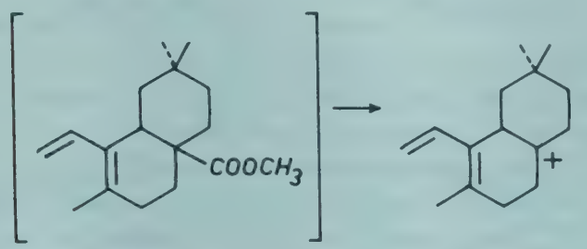
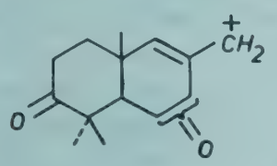


I. $R_1 = R_2 = O, R_3 = R_4 = O, R_5 = H$
II. $R_1 = R_2 = O, R_3 = R_4 = O, R_5 = CH_3$
III. $R_1 = H, R_2 = OH, R_3 = H, R_4 = OH, R_5 = CH_3$
IV. $R_1 = H, R_2 = OAC, R_3 = H, R_4 = OAC, R_5 = CH_3$



a, m/z 262 b, m/z 203



c, m/z 219

SCHEME I

3.60 (see ref. 15). The PMR spectrum of the diene did not display the presence of any D_2O exchangeable proton. Moreover, the spectrum exhibited a two-proton multiplet centered at δ 2.40 for methylene protons at C-6 as in the case of xanthoxylone[16]. This observation led to confirm that the second carbonyl in methyl rubonate (II) or rubonic acid (I) was situated at C-7 and not at C-6. On the basis of the above observations and also the fact that KBH_4 reduction product of methyl rubonate (II) was identical with methyl canthate[5] proved beyond doubt that rubonic acid can be represented by structure (I).

Our thanks are due to Prof S C Bhattacharyya, IIT, Bombay and to Prof B B Biswas, and Prof S K Sen of our Institute for their interest in the work. We are also thankful to Drs K L Ghatak and E T H Zurich for mass and PMR spectra.

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New Photometabolites of Endrin†

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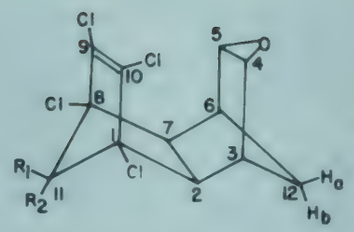
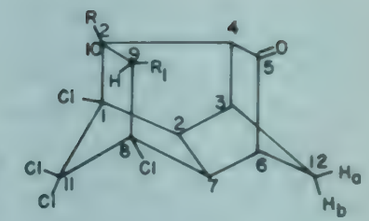
Photolysis of endrin (**1**) for longer duration (24 hr) in acetone yields three new metabolites formed by further loss of one chlorine atom from positions-11 (*syn* and *anti*) and 9 of initially produced photoendrin (**2**). Their structures (**7-9**) are based on spectroscopic evidences reported.

Endrin (**1**), one of the principle cyclodiene insecticides, is not only persistent but is reported to form toxic photometabolites, as a result of which its agricultural use is now restricted in many countries. Because of its notoriety as environmental pollutant, the phototransformations of **1** has been well investigated by a large number of workers. The major well characterised photometabolites of **1** are, δ-keto photoendrin[1] (**2**) and the half cage keto product (**5**)[2] formed by loss of chlorine atom from the C-10 bridge-head of **2**. Two other minor metabolites **3** and **4** have also been identified[3] from solid state photolysis of **1**. Very recently another photoproduct **6**, formed by stereo-selective photodechlorination of syn chlorine atom of the methano bridge of **1**, has been described[4]. In connection with another work large quantities of **2** were needed and during its preparation, the presence of several hitherto unidentified minor metabolites in the mixture became evident. In this note we report the isolation and structures of three new photometabolites formed by irradiation of **1** in acetone.

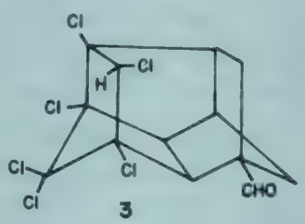
Irradiation of a solution of **1** in acetone in a water-cooled quartz cell with light from a high pressure Hg lamp for 24 hr, yielded, besides **2** as the major product, three new minor metabolites separable by column chromatography on silica gel. The first one, a microcrystalline solid, m.p. 178-80°, is formed by loss of one chlorine atom as evidenced by its mass spectrum. The presence of a strong fragment at *m/z* 316 ($M^+ - CO$) and a peak at 1725 cm^{-1} in its IR spectrum due to $\nu C=O$, showed that it is a cyclic ketone related to photoendrin (**2**) Structure **7** for this new metabolite could be arrived at one the basis of its PMR spectrum which was practically similar to that of **2** but showed the presence of a new one-proton singlet at δ4.85 assignable to the syn proton of the methano bridge at C-11 of **7**. Structure **7** for this metabolite



1, $R_1 = R_2 = Cl$
6, $R_1 = H$; R_2 Cl
10, $R_1 = Cl$; $R_2 = H$



2, $R_1 = R_2 = Cl$
5, $R_1 = Cl$; $R_2 = H$
9, $R_1 = H$; $R_2 = Cl$



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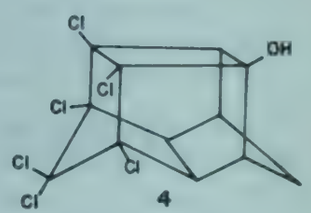

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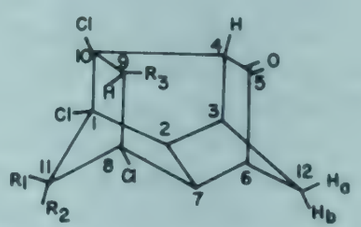

7, $R_1 = H$; $R_2 = R_3 = Cl$
8, $R_1 = R_3 = Cl$; $R_2 = H$

was finally confirmed when **6**, obtained earlier[4] by amine-induced photolysis of **1**, gave **7** on irradiation under acetone-sensitised condition. The two products were formed to be identical in all respects.

The second metabolite, a crystalline compound, m.p. 208-10°, was isomeric with **7**, as could be readily deduced on the basis of its mass spectrum (formation from **2** by loss one Cl atom) and IR spectrum (carbonyl peak at 1725 cm^{-1}, cyclic ketone). Its PMR spectrum exhibited a new one-proton singlet at δ 4.50 assignable to the *anti*-proton of the methano bridge at C-11 of **8**. Structure **8** was further confirmed when **10**, obtained earlier from endrin (**1**) by superoxide-induced dehalogenation[5], could be readily isomerised to **8** on irradiation under sensitised condition.

The third new minor metabolite isolated from the mixture was considered to have structure **9** as its mass and IR spectra revealed that it had the skeleton of **2**; its PMR spectrum, however, was devoid of a one-proton singlet at δ 4.90 present in **2**. Instead the PMR dis-

†Communication No. 338.

played a new two-proton double doublet at δ 2.02 (J = 10.5 Hz). This high field doublet could be assigned to the two protons at C-9 of structure **9**. Evidently it is formed from **2** by the loss of one Cl atom from C-9 position.

Thus photoendrin (**2**), formed initially from **1**, undergoes further loss of one chlorine atom on longer irradiation in acetone from different positions giving **7**, **8** and **9**.

PMR spectra were recorded in $CDCl_3$ at 60 MHz on a Varian KM 360L spectrometer with THS as on internal reference. Mass spectra were recorded on a Jeol JMS-D300 spectrometer in the El mode.

Photolysis of endrin (**1**) *in acetone*

A solution of **1** (1 g) in distilled acetone (500 ml) was irradiated in a quartz cell with light from Hg lamp for 24 hr. The solvent was removed under reduced pressure and mixture was chromatographed over a silica gel (100 g) column. The column was eluted with (i) hexane-benzene (4 : 1), 200 ml (8 fractions of 25 ml each); (ii) hexane-benzene (1 : 1), 200 ml (4 fractions of 50 ml each); and (iii) benzene (200 ml).

The first four fractions of eluate (i) were combined and the solvent removed when it yielded **7** as a grey solid (75 mg) which crystallised from methanol as microcrystalline solid, m.p. 178-80° (Found: C, 41.0; H, 2.5. $C_{12}H_8Cl_5O$ requires C, 41.1; H, 2.3%); MS: *m/z* 344 (M^+) 316 ($M^+ - CO$), 309 ($M^+ - Cl$); PMR: δ 5.0 (1H, *s*, H-9); 4.85 (1H, *s*, H-11), 3.41 (1H, *s*, H-2), 3.35 (1H, *s*, H-7); 3.22 (1H, *s*, H-4), 3.15 (1H, *s*, H-3), 2.80 (1H, *s*, H-6), 1.8-1.0 (2H, *dd*, J = 11 Hz, H-12a and 12b).

The next four fractions of eluate (i) combined gave on solvent removal photoendrin **2** (500 mg), m.p. 280°(d).

The hexane-benzene (1 : 1) eluate (ii) were combined and solvent removed when it gave **8** (150 mg). It crystallised from hexane-benzene as colourless needles, m.p. 207-10° (Found: C, 41.4; H, 2.2. $C_{12}H_8Cl_5O$ requires C, 41.1; H, 2.3%); MS: *m/z* 344 (M^+), 316 ($M^+ - CO$), 309 ($M^+ - Cl$); PMR: δ 4.90 (1H, *s*, H-9), 4.52 (1H, *s*, H-11), 3.40 (1H, *s*, H-2), 3.32 (1H, *s*, H-7), 3.20 (1H, *s*, H-4), 3.05 (1H, *s*, H-3), 2.90 (1H, *s*, H-6), 1.8-1.5 (2H, *dd*, J = 11 Hz, H-12a and 12b).

The benzene eluate (iii), on removal of benzene, gave **9** as a colourless solid (75 mg). It crystallised from methanol as colourless prisms, m.p. 195° (d) (Found: C, 41.5; H, 2.4. $C_{12}H_8Cl_5O$ requires C, 41.1; H, 2.3%); MS: *m/z* 344 (M^+), 316 ($M^+ - CO$), 309 ($M^+ - Cl$); PMR: δ 3.40 (1H, *s*, H-2), 3.32 (1H, *s*, H-7), 3.28 (1H, *s*, H-4), 3.10 (1H, *s*, H-3), 2.50 (1H, *s*, H-6), 2.02 (2H, *dd*, J = 10.5 Hz, H-9a and 9b), 1.05-0.80 (2H, *dd*, J = 11 Hz, H-12a and 12b).

We thank the ICAR, New Delhi for financial support.

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Synthesis of 2,8-Disubstituted 3,7-Dimethoxy-4,6-dioxo-4*H*,6*H*-benzo[1,2-*b*:5,4-*b*']dipyrans as Potential Insecticides

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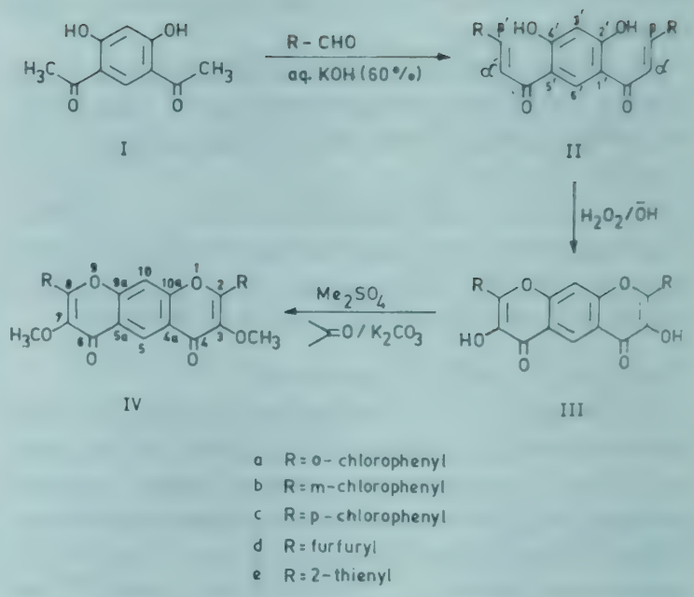
Some new linearly fused benzo-γ-dipyrones have been prepared in good yields from 5-acetyl-2,4-dihydroxyacetophenone (I) and characterised by their spectral data. The fish-toxicity and antifeedant activity of the title compounds have been studied.



It is reported in literature that the linearly fused benzo-γ-dipyrones are more active than the angularly fused analogues in a number of physiological activities[1]. For example disodium 4,6-dioxobenzo[1,2-*b*:5,4-*b*']dipyran-2,8-dicarboxylate is several times more active than the corresponding angular compound[2]. Therefore, in the present investigation some new linearly fused benzo-γ-dipyrones bearing halogenophenyl or heterocyclic moiety have been synthesised, and their fish-toxicity and antifeedant activity studied.

5-Acetyl-2,4-dihydroxyacetophenone (I)[3] was condensed with various aromatic aldehydes (*o*-chloro-, *m*-chloro- and *p*-chlorobenzaldehydes, furfural and thiophene-2-aldehyde) in the presence of 60% aq. KOH to yield the corresponding dichalcones (IIa-e, yield 70-80%) (Table 1) which gave deep red colouration with conc. H_2SO_4 and reddish brown colouration with ethanolic $FeCl_3$ in support of their structure. The structures of these dichalcones were established by elemental analyses and spectral data. As a representative case, spectral data of 2,4-di(*o*-chlorocinnamoyl)resorcinol (IIa) have been given here. The IR(KBr) spectrum of IIa exhibited chelated carbonyl and *trans*−CH=CH− bands at 1622 and 960 cm^{-1} respectively. In the UV(MeOH) spectrum, absorption bands appeared at 208 (log ε 4.53), 242 (4.17), 315 (4.43) and 370 nm (4.10), similar to those of chalcones[4]. The PMR($CDCl_3$) spectrum of IIa displayed two doublets at δ 7.48 (J=17 Hz) and 8.2 (J=17 Hz), integrating for two protons each, which were assigned to α,α'- and β,β'-protons respectively. The spectrum also exhibited two sharp singlets at δ 6.48 and 8.46 each integrating for one proton which were assigned to 3'- and 6'-protons respectively. The singlet at δ 13.3 (2H, D_2O exchangeable) was assigned to chelated hydroxyls on C-2' and C-4'. Besides these, two multiplets appeared at δ 7.3 (6H; 4,4'' 5,5'' and 6,6'' protons) and 7.65 (2H; 3,3'' protons). The mass spectrum of compound IIa showed $M^{+\cdot}$ at *m/z* 438 (21%) and the prominent ions at *m/z* 402 (100%) and 403 (29%) which are probably formed by the loss of HCl and Cl radicals respectively. The ions at *m/z* 300 (5%) and 138 (18%) arise due to RDA of isomeric flavanone. The ^{13}C NMR spectrum of IIa showed eleven signals assignable to twenty four carbon atoms of IIa. The signals at δ 138.48 and 114.86 were readily assigned to β,β' and α,α' carbons respectively and that at 191 to the carbonyl carbons. Other signals appeared at δ 100.56 (C-1', 3', 5'), 124.83 (C-2,2''), 127.43 (C-3,3'', 5,5''), 128.67 (C-1,1''), 129.81 (C-6,6''), 131.87 (C-6'), 134.20 (C-4,4'') and 167.74 (C-2',4'). This appears to be the first report on ^{13}C NMR spectrum of a compound of this type.

The dichalcones (II) on Algar-Flynn and Oyamada oxidation[5,6] using alkaline H_2O_2 gave the corresponding 2,8-disubstituted 3,7-dihydroxy-4,6-dioxo-4*H*,6*H*-benzo[1,2-*b*:5,4-*b*']dipyrans (IIIa-e) in better yields at room temperature rather than at 0°. These dihydroxybenzodipyrones (III) were soluble in 1% aq. NaOH and gave colouration with ethanolic $FeCl_3$ characteristic of phenolic groups. These compounds also gave a pink colouration in Shinoda test[7], indicating their flavonoid nature. As a representative case, the spectral data of 2,8-di-(*o*-chlorophenyl)-3,7-dihydroxy-4,6-

Table 1—Physical, Spectral and Biological Data of the Various Compounds Prepared

Compd*†	m.p. °C	Yield (%)	$M^{+\cdot}$ (abundance)	UV(MeOH) λ_{max} (log ε) nm	Fish Toxicity		% Antifeedant activity
					time min-sec	Survival time min-sec	
IIa	210	80	438 (21.3%)	208 (4.53) 242 (4.17) 315 (4.43) 370 (4.10)	06-03	124-50	88.88
IIb	190	71	438 (27.7%)	204 (4.30) 248 (4.38) 312 (4.38) 372 (3.96)	10-03	129-10	92.54
IIIc	232	76	438 (58.1%)	205 (4.37) 254 (4.24) 320 (4.37) 369 (4.06)	07-13	145-26	92.85
IId	200	75	350 (81.5%)	206 (4.22) 265 (4.07) (348 (4.40) 390 (4.18)	05-05	56-03	87.46
IIe	234	70	382 (100%)	202 (4.08) 288 (4.03) 350 (4.37) 390 (4.14)	04-29	46-50	94.13
IIIa†	253	50	466 (11.1%)	208 (4.48) 268 (4.25) 362 (3.97)	05-05	39-21	95.55
IIIb	228	30		213 (4.37) 263 (4.32) 361 (3.89)	06-29	47-00	91.58
IIIc	261	41		207 (4.45) 267 (4.35) 368 (3.88)	08-12	50-13	96.50
IIId	272	46	378 (5%)	213 (4.39) 270 (4.22) 363 (4.23)	04-49	32-41	81.43
IIIe	225	40	410 (5%)	213 (4.48) 266 (4.18) 364 (4.36)	04-18	42-16	89.05
IVa§	205	70	495 (15%)	206 (4.40) 265 (4.38) 325 (3.97)	04-47	35-25	90.31
IVb	200	62		205 (4.45) 264 (4.40) 321 (3.85)	05-13	49-37	92.22
IVc	227	67		203 (4.45) 264 (4.40) 326 (4.00)	05-17	44-20	96.82
IVd	212	65		204 (4.31) 248 (4.36) 329 (4.14)	04-30	22-45	92.69
IVe	240	60		202 (4.35) 249 (4.38) 330 (4.16)	04-15	13-07	97.14

*All the compounds gave satisfactory C and H analyses.

†Solvents used for crystallisation were: $CHCl_3$ for IIa; EtOH – $CHCl_3$ for IIb: EtOH for IIc and IIe; C_6H_6 for IId.

§PMR (DMSO – d_6): δ 7.61 (*m*, 8H, 2 × *o*-Cl – C_6H_4 –), 9.97 (*s*, 1H, H-10), 8.93 (*s*, 1H, H-5), 9.64 (*s*, 2H, D_2O exchangeable, C_3 – OH and C_7 – OH); ^{13}C NMR(DMSO – d_6): δ 106.41 (C-10), 119.68 (C-4a, 5a), 124.10 (C-5), 124.73 (C-6′,6″), 127.26 (C-1′,1″), 129.70 (C-4′,4″), 131.98 (C-3′,3″,5′,5″), 132.79 (C-2′.,2″), 138.97 (C-3,7), 146.99 (C-2,8), 156.74 (C-9a,10a), 173.88 (C-4,6); MS: *m/z* 465 (M – 1: 31%), 432 (M – 2 × OH: 37): 431 (M – Cl: 30), 430 (M – HCl; 100), 394 (M – 2HCl; 22), 198 [M – (2HCl + 2H); 40].

§PMR(DMSO-d_6): δ 3.84 (*s*, 6H, C_3- and C_7 – OCH_3), 7.26 (*s*, 1H, H-10), 7.5 (*m*, 8H, 2 × *o*-Cl – C_6H_4 –), 9.27 (*s*, 1H, C_5 – H); MS: *m/z* 493 (M – H; 28%), 492 (M – 2H: 30), 459 (M – Cl; 10), 458 (M – HCl: 16), 456 [M – (HCl + 2H); 45], 455 (456 – H; 100), 277 [doubly charged (456 – H): 15].

dioxo-4*H*,6*H*-benzo[1,2-*b*; 5,4-*b*']dipyran (IIIa) are given in Table 1.

The dipyrones (III) on methylation with dimethyl sulphate and anhyd. K_2CO_3 in dry acetone yielded the corresponding dimethyl ethers (IVa-e) which were not soluble in 1% aq. NaOH and did not give colouration with ethanolic $FeCl_3$. Their structures were established by elemental analyses and spectral data. As a representative case, the spectral data of 2,8-di-(*o*-chlorophenyl)-3,7-dimethoxy-4,6-dioxo-4*H*,6*H*-benzo[1,2-*b*:5,4-*b*']dipyran (IVa) are given in Table 1.

All the compounds synthesised were tested for their fish-toxicity following the "Survival time method" of Powers[8] and Gersdorff[9] as well as by the "Turning time method" of Krishnaswami and Seshadri[10] using rotenone as standard. The fish species *Cyprinus carpio communis* and *Oreochromic mossambicus* were employed as test animals for evaluating turning time and survival time respectively. The antifeedant activity of the above compounds was assessed by "Non-choice test method"[11] using six-hour prestarved fourth instar larvae of *Spodoptera litura*. The results are given in Table 1. The present study reveals that 2,8-di-(2-thienyl)-3,7-dimethoxy-4,6-dioxo-4*H*,6*H*-benzo[1,2-*b*:5,4-*b*']dipyran (IVe) exhibits highest fish-toxicity and antifeedant activity.

Dichalcones (*IIa-e*): *General procedure*

A mixture of I (0.01 mol) and the appropriate aldehyde (0.02 mol) in ethanol (40 ml) was kept at room temperature for 12 hr with aq. KOH (60%, 10 ml). The product, obtained on dilution and acidification with dil. HCl, was subjected to column chromatography over silica gel (200 mesh). The benzene-chloroform (8:2, v/v) eluates on concentration afforded II (Table 1).

2,8-*Disubstituted* 3,7-*dihydroxy*-4,6-*dioxo*-4*H*,6*H*-*benzo*[1,2-*b*:5,4-*b*']*dipyrans* (*IIIa-e*): *General procedure*

To a mixture of II (2 g), ethanol (30 ml) and 20% aq. NaOH (30 ml) at room temperature, was added 30% H_2O_2 (6 ml) with constant stirring. The reaction mixture was kept aside overnight and acidified with acetic acid. The solid that separated was washed with water and crystallised from ethanol to get III (Table 1).

2,8-*Disubstituted* 3,7-*dimethoxy*-4,6-*dioxo*-4*H*,6*H*-*benzo*[1,2-*b*:5,4-*b*']*dipyrans* (*IVa-e*; *Table* 1): *General procedure*

A mixture of III (0.3 g), dry acetone (200 ml), dimethyl sulphate (1.5 ml) and ignited K_2CO_3 (5 g) was refluxed for 6 to 8 hr. Usual work-up of the reaction mixture gave the corresponding dimethyl ether (IV), which crystallized from ethanol.

We are grateful to Prof. B Sethuram, Head of the Department of Chemistry, for providing facilities, Dr D S Bhakuni, RSIC, Lucknow for PMR spectra and to Dr A V Rama Rao, Director, RRL, Hyderabad for ^{13}C NMR spectra. One of us (D A) is grateful to CSIR, New Delhi for the award of a senior research fellowship.

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BOOK REVIEWS

Design and Synthesis of Organic Molecules Based on Molecular Recognition (Proceedings of the XVIIIth Solvay Conference on Chemistry), edited by G van Binst (Springer-Verlag, Berlin, Heidelberg), 1986, pp. 315. Price DM 166.

The Solvay Conferences conjure up images of the heroic days of Physics in the period between 1910 and 1930 and it might surprise readers that the meetings encompass organic and biological chemistry. Beginning with the preface by Vladimir Prelog and the introduction by Ephraim Katchalski-Katzir, this is a book which should be read by all aspiring and practising bioorganic chemists. Biochemistry provides a spectacular scenario of molecular recognition and specificity of chemical reactions. It is little wonder that mimicking Nature's chemistry affords a remarkable challenge to contemporary organic chemistry. This book summarizes the work of many leading practitioners of biomimetic chemistry and also provides exciting glimpses into biological problems awaiting attack from a more chemical perspective. The articles based on lectures have been divided into four groups: (1) Molecular recognition in biochemical processes; (2) thermodynamics, kinetics and stereochemistry in molecular recognition; (3) synthetic models of "hosts"; and (4) design of new guests. Short reports and the discussions following the lectures are also presented. These sometimes form a most illuminating section of the book.

Some talks (e.g. Schwyzer on Peptide-membrane interactions; and Huber on Protein flexibility) have been condensed to an extent that little can be gleaned about these topics. In contrast, others (e.g. Karplus on Protein-ligand binding; Scheraga on Molecular recognition; and Cram on Hostguest relationships) are more detailed and constitute useful reviews. In some, the discussion mirrors the sharp controversies that exist in these areas (cf intervention by Wodak on p. 135 following Scheraga's talk where the problems of "docking" in computational studies of molecular interactions are considered). Readers would do well to remember that the chemical elegance of synthetic host design (synthetic enzymes of the future?) a la Cram, Lehn and Breslow often masks the complexities of modelling enzymatic processes. The recent demonstration of the "p-nitrophenyl ester syndrome" by Menger [*J Am chem Soc*, **109** (1987) 3145-3146] provides a salutary lesson that organic chemistry is still far from understanding Nature's molecular design strategies.

The extraordinarily wide scope of the articles in this book (for example, biomimetic reactions, molecular design, binding processes and crystal engineering) make this volume most attractive for browsing. Its broad interdisciplinary style will hopefully kindle new ideas in a field which sometimes appears to be mired in complexity. Will synthetic tailor made model enzymes eventually function as efficiently as their macromolecular counterparts? This is a question central to many of the areas covered in the XVII Solvay Conference. This book does not provide an answer but much of its contents must be carefully considered in chalking out future strategies.

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Non-Traditional Oilseeds and Oils in India, edited by N V Bringi (Oxford & IBH Publishing Co., New Delhi), 1987, pp. ix + 254. Price Rs 85.

This book is sponsored by the Kane Memorial Trust in memory of Prof J G Kane who had contributed greatly to the understanding, processing and utilisation of a large number of less-known, minor, non-traditional, tree-borne oilseeds of mostly forest origin The book carries a foreword, appreciative of the Editor and the contents, by S. Varadarajan.

The book is divided into ten chapters: (1) Sal (*Shorea robusta*) seeds fat (55 pages); (2) *Madhuca indica* seed fat—mowrah (17 pages); (3) Mango (*Mangifera indica*) kernel fat (24 pages); (4) *Garcinia indica* Choisy (kokum), *Vateria indica* (dhupa) and *Bassia butyracea* (phulwara) seed fats (21 pages); (5) Neem (*Azadirachta indica* Juss) seed oil (25 pages); (6) Karanja seed (*Pongamia glabra*) oil (24 pages); (7) Kusum seed (*Schleichera trijuga*) oil (25 pages); (8) *Salvadora oleoides* and *Salvadora persica* (khakan or pilu) seed fat (9 pages); (9) Pisa (*Actinodaphne hookeri*) seed fat (15 pages); and (10) Lesser known tree-borne oilseeds (33 pages). A combined index of authors and subjects is provided at the end (6 pages). Except for the chapter 3 (by D.K. Bhattacharyya) and

chapter 9 (by V V R Subrahmanyam) all the other chapters are either authored (chapters 1, 8 and 10) or co-authored (chapters 2, 4-7) by the Editor, the co-authors being D T Mehta (chapters 2 and 4), M S Thakur (chapter 5), S K Mukherjee (chapter 6) and M G Kasbekar (chapter 7).

Each chapter covers description of tree, fruit, seed and kernel, occurrence, availability, collection and storage of seeds, production of oil, nature and composition of constituent fatty acids, glycerides and non-glyceride components of oil, processing and utilisation of oil, and composition and utilisation of oil-cake or deoiled meal. Most of these non-traditional tree-borne oilseeds of mainly forest origin contain unusual components which contribute to dark colour, bad odour, bitter taste and toxicity. The nature of such components is discussed thoroughly with illustration of structures and methods for their characterization and removal.

The first four chapters deal with vegetable butters and naturally emphasis is given to purification, fractionation, evaluation and use of these fats as cocoa butter equivalents. Importance is also given to the pesticidal constituents in neem and karanja oils. Cyanolipids in kusum oil and other unusual lipids in some less known oilseeds have also received adequate coverage. The last chapter deals briefly with eleven oilseeds which are known but exploited to a lesser extent than those covered in the other chapters because of inadequate availability and collection. These are: *Citrulus colocynthis* (thumba), *Butea frondosa* (palash), *Calophyllum inophyllum* (undi), *Mesua ferrea* (nahor), *Jatropha curcas* (ratanjyot), *Hevea brasiliensis* (rubber), *Hydnocarpus wightiana* (maroti), *Mallotus philippensis* (kamala), *Garcinia cambogia* (dharambe), *Garcinia morella* (gamboge) and *Celastrus paniculaturs* (malkanguni). These non-traditional oils which vary widely in nature have received much attention in India because of shortage of vegetable oils for edible and industrial purposes. These are also of universal interest in view of the occurrence of unusual components with proven or potential biological applications.

The authors have not only covered the subject matter logically in a readable manner but have also given leads for further research. Most of the sources of informatiopn covered in this book are either the papers published in the Indian journals or presented in symposia/seminars held in India or unpublished reports from the organisations, in which the authors have worked. Naturally, only Indian authors could have written such chapters. This book is thus especially useful for foreigners who would otherwise find it difficult to have access to such information.

The book could be still better if some minor omissions or commissions have not been made. Often it has not been stated whether fatty acid composition reported is mole or weight per cent. Abbreviations such as TLC, IV (though common and well known) should have been elaborated when they occur for the first time or given separately in an appendix. Structures of fatty acids should also have been given to make the book-self-contained. It is surprising that the other commonly known name 'mahua' for 'mowrah' is not mentioned. In a few places, uniformity in format of references and abbreviations is lacking. Some grammatical and printing errors are also noticed. The official addresses of authors should have been included for convenience of the readers. The information is not up to date on a few aspects. Some important references do not find a place while some not-so-relevant ones do. "Lipid associates" is more appropriate and more commonly used term than "non-lipid associates" to describe the non-fatty, unusual components found in these seed oils. These minor criticisms are only for improvement in the future edition and do not anyway minimise the value of the book.

The book is recommended for all those who have anything to do with chemistry and technology of oils, fats and other lipids and oilcakes. Entomologists, biochemists, nutritionists, toxicologists, agricultural scientists, afforestation agencies, government planners, and industrialists dealing with oils, soaps, surface coatings, insecticides, pharmaceuticals and confectionaries will also find the book useful.

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